

Pharmacological Potential of Benzamide Analogues and their Uses in Medicinal Chemistry

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Abstract

Benzamide derivatives possess different kinds of pharmacological activities like antimicrobial, analgesic, anti-inflammatory, anticancer, cardiovascular, and other biological activities. Due to these biological significances, scientists have interesting to develop various new benzamide derivatives. There is still need to improve the already used benzamide derivatives and search for the new and more effective benzamide derivatives. This review exhibited various pharmacophoric activities of benzamides analogues which are biologically importance.

Keywords: Benzamide; Pharmaceutical applications; Biological activity

Introduction

Benzamide is a carbonic acid amide of benzoic acid. Amide is a group of organic chemicals with the general formula RCO-NH_2 in which a carbon atom is attached to oxygen in double bond and also attached to an hydroxyl group, where 'R' groups range from hydrogen to various linear and ring structures or a compound with a metal replacing hydrogen in ammonia such as sodium amide, NaNH_2 . Amides are divided into subclasses according to the number of substituents on nitrogen. The primary amide is formed by replacement of the carboxylic hydroxyl group by the NH_2 amino group. An example is acetamide (acetic acid+amide). Amide is obtained by reaction of an acid chloride, acid anhydride, or ester with an amine. Amides are named with adding '-ic acid' or '-oic acid' from the name of the parent carboxylic acid and replacing it with the suffix 'amide'. Amide can be formed from ammonia (NH_3). The secondary and tertiary amides are the compounds in which one or both hydrogens in primary amides are replaced by other groups. The names of secondary and tertiary amides are denoted by the replaced groups with the prefix capital N (meaning nitrogen) prior to the names of parent amides. Low molecular weight amides are soluble in water due to the formation of hydrogen bonds. Primary amides have higher melting and boiling points than secondary and tertiary amides.

Medicine materials

In psychiatry and related medical fields, two active substances from the group of Benzamides are in use Sulpiride and Amisulpiride. Another benzamide, Remoxipride was taken off the market in 1993 because of life threatening side effects.

Biological Profile

Anticonvulsant activity

A comparison of enamines from various unsubstituted and p-substituted benzamides to the analogues benzyl amines has been undertaken with the aim of elucidating the essential structural parameters necessary for anticonvulsant activity [1]. Initial studies on methyl 4-N-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-ate, (Scheme 1), 3-N-(benzylamino) cyclohex-2-en-1-one (Scheme 2) and 5,5-dimethyl-3-N-(benzylamino)-cyclohex-2-en-1-one Scheme 3 indicated that benzylamines possessed significant anti-maximal electroshock seizure (MES) activity. Evaluation of the analogous benzamides revealed significant differences in their three dimensional structures. A series of N-(tetrahydroisoquinolinyl)-2-methoxybenzamides by high throughout screening at the novel SB-204269 binding site, the structure activity relationship (SAR) studies

have provided compound (Scheme 4) with high affinity and good anticonvulsant activity in animal models [2]. The anticonvulsant N-(5-methylisaxazol-3-yl)-2,6-dimethylbenzamide (D2916), which presents two kinds of methyl groups which could be oxidized, was submitted to various chemical oxidizing agents. Several sites and degrees of oxidization were observed. The main oxidized site was the aryl methyl group without cleavage of the isoxazole ring, leading via carboxylic acid and primary alcohol intermediates to phthalimide and lactame derivatives. In no case was the methyl group of the isoxazole moiety hydroxylated [3]. A study on the anticonvulsant properties of 4-amino-N-(2-ethylphenyl) benzamide (4-AEPB) (Scheme 5), in screening mice was dosed interperitoneally (i.p.), revealed that 4-amino-N-(2-ethylphenyl) benzamide (4-AEPB) was active in MES test at the dose of 10 and 100 mg/kg after 30 mins and 4 h, respectively against phenytoin [4,5]. A series of benzamides containing N,N-2-trimethyl-1,2-propane diamine as the amide moiety, the compounds were tested in the MES and pentylenetetrazole (metrazole, MET) screens for anticonvulsant activity. The 3,5-trifluoromethyl-3,5-dichloro, and 3-bromo analogues proved to be either equipotent with or more potent than phenytoin. A short series of 4-nitro-N-phenylbenzamides (Schemes 6 and 7) was evaluated for anticonvulsant properties and neurotoxicity in mice dosed i.p., three of the four 4-nitro-N-phenylbenzamides were efficient in the MES test, especially N-(2,6-dimethylphenyl)-4-nitrobenzamide (ED_{50} value in the MES test=31.8 $\mu\text{M}/\text{kg}$, TD_{50} =166.9 $\mu\text{mol}/\text{kg}$, protective index (PI)=5.2) and N-(2-chloro-6-methylphenyl)-4-nitrobenzamide (ED_{50} value in the MES test=90.3 $\mu\text{mol}/\text{kg}$, TD_{50} =1.068 $\mu\text{M}/\text{kg}$, PI=11.8). The latter 4-nitro-N-phenylbenzamide was also found to be active against seizures induced by scPTZ and was selected for further evaluation in rats dosed orally. In these conditions, N-(2-chloro-6-methylphenyl)-4-nitrobenzamide was found to be, three times more active than phenytoin and 4-amino-N-(2,6-dimethylphenyl) benzamide, two times more potent in the MES test [6].

Anti-inflammatory activity

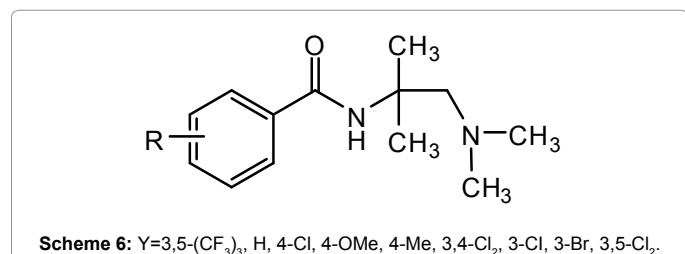
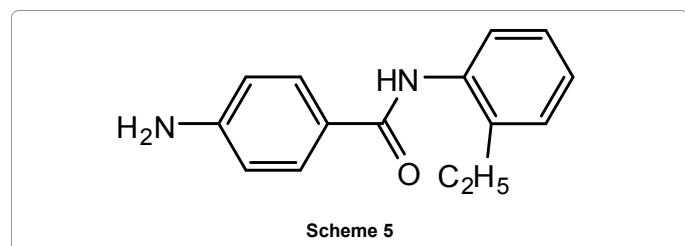
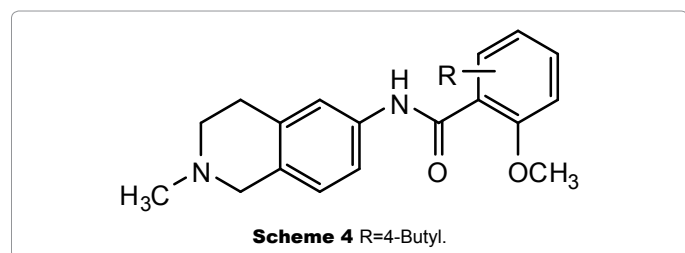
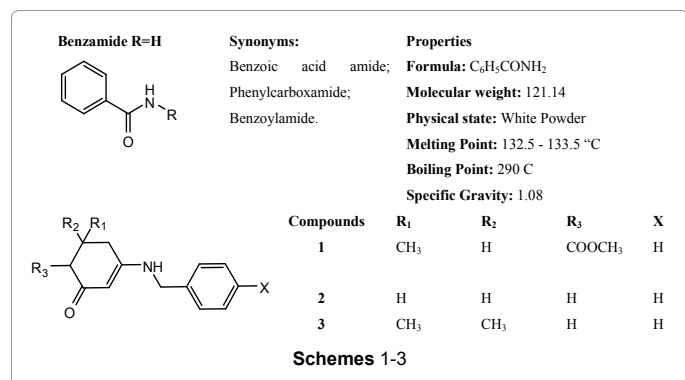
Parsalimide (5-amino-N-butyl-2-(2-propynyloxy) benzamide) (Scheme 8), is a nonsteroidal antiinflammatory drug (NSAID),

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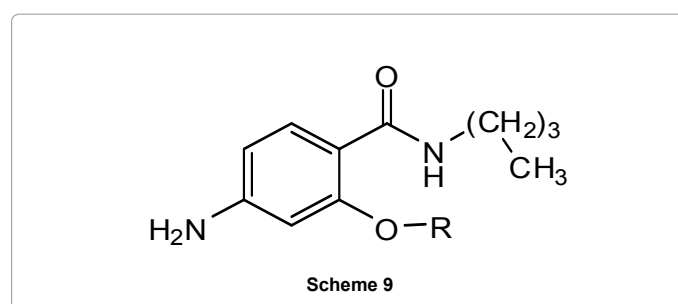
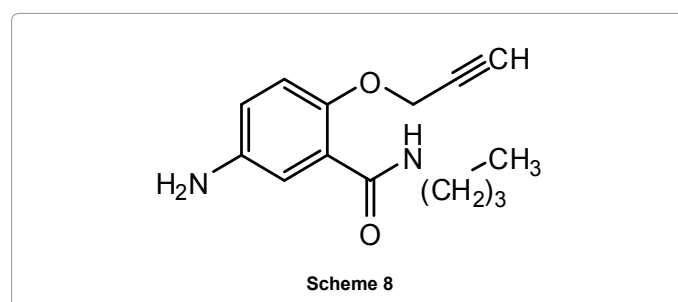
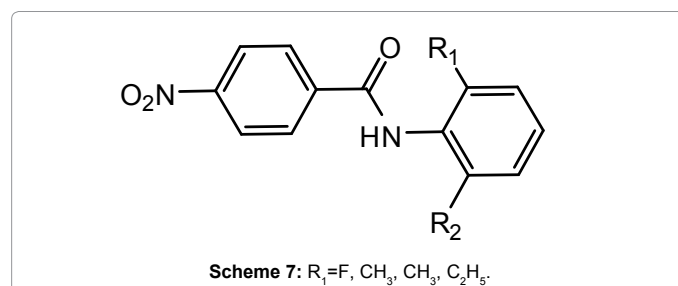


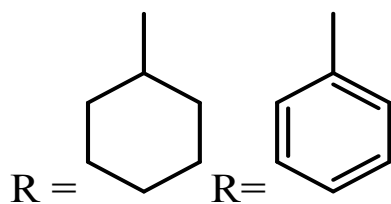
commercialized in Italy until 1985 with the brand name of Synovial, that has been widely used to treat arthritic patient. In addition, it was shown to spare gastric mucosa. A series of novel substituted benzamides, related to Parsalimide, and have evaluated their activity *in vitro* on COX-1 and COX-2 as well as *in vivo* in the Carragenan-induced rat paw edema, a classical *in vivo* anti-inflammatory assay. Compounds (Schemes 9 and 10), which showed a favorable profile *in vitro* and *in vivo*, were screened in comparison with parsalimide for gastrointestinal (GI) tolerability *in vivo* in the rats. Results obtained showed that Parsalimide and compound (Scheme 10) inhibited both COX-1 and COX-2 *in vitro* as well as they were active *in vivo*. Both compounds were devoid of gastric effect at the efficacious dose. In addition, both prevented indomethacin induced gastric damage [7]. Two series of N-[4-(alkyl) cyclohexyl]-substituted benzamides, i.e., a series of N-[4-(tert-butyl) cyclohexyl]-substituted benzamides (Scheme 11a-11h) and a series of N-[4-(ethyl) cyclohexyl]-substituted benzamides (Scheme 12a-12h) were tested for their anti-inflammatory and analgesic potencies, and gastro-intestinal irritation liability. As

regards the anti-inflammatory activity, best results were shown by Scheme 11f, followed by Scheme 11d but many other compounds showed pharmacological potency. As regards the ulcerogenic action, the most potent compound was Scheme 12d, followed by Scheme 11c and 11f, but in general all compounds showed a high irritative capacity.

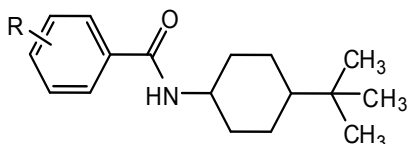
Analgesic activity

To explore the structure activity relationship (SAR) of a series of potent opioid agonists. Series of tropanylidene benzamides synthesized by N-ethyl-4-[(8-phenethyl-8-aza-bicyclo [3.2.1] oct-3-ylidene)-phenyl]-methyl)-benzamide (Scheme 13) proved extremely tolerant of structural variation while maintaining excellent opioid activity [8,9]. A subset was tested orally at 150 μmol/kg in the mouse, 48°C hot plate test, some compounds provided robust anti nociception and most induced Straub tail, a behavior often associated with ju opioid agonist activity. The 3 and 4-carboxy phenyl tropanylidenes provided little or no analgesic effects in the same testing paradigm most likely due to poor oral absorption or brain penetration and observed no instances of convulsions or deaths with these compounds. A series of N,N-dialkyl-4-((8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl) benzamides, the lead compounds bind with exceptionally high affinity to the δ opioid receptor and were also highly selective for δ versus μ opioid binding. They were full δ agonists and were antinociceptive in the mouse abdominal irritant test. They appear to have a lower convulsant liability than earlier δ agonists. The δ opioid agonists have been seen as potentially safer alternatives to conventional agonists as pain relieving agents. Alternative therapeutic roles for these agents, in neuropathic or inflammatory pain, depression, parkinson's disease and

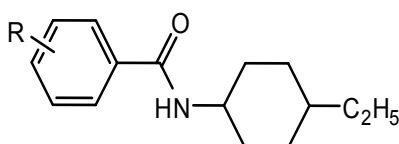




Scheme 10

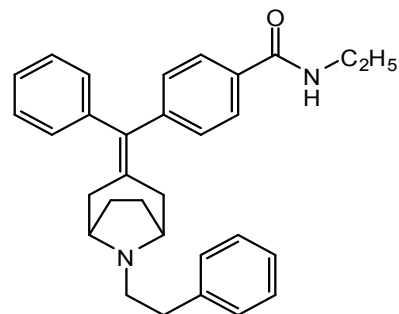


Scheme 11a-h



a: R= 3,4,5-(CH₃O)₃; b: R=4-Cl; c: R=4-F;
d: R=4-Br; e: R=2,4-Di-Cl; f: R=H; g:R=4-CH₃; h:R=4-NO₂

Scheme 12a-h



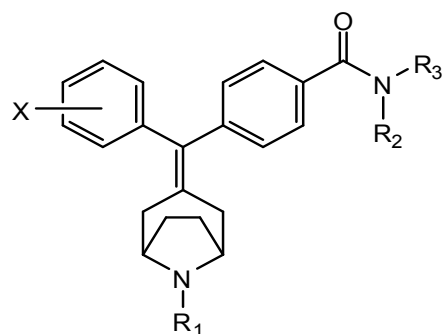
Scheme 13

lung cancer have been suggested [10]. N-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene) phenylmethyl]-benzamides, the tertiary amide 6 opioid agonist (Scheme 14) was a potent antinociceptive agent. Compound (Scheme 14) was metabolized *in vitro* and *in vivo* to secondary amide, a potent and selective μ opioid agonist. The SAR of a series of N-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene) phenylmethyl] benzamides was also tested [11].

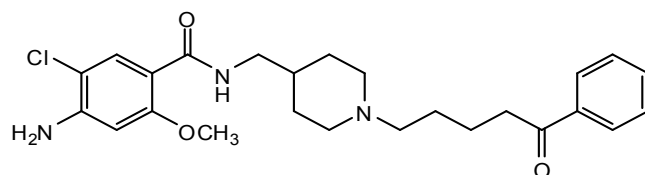
Serotonin (5-HT) activity

Serotonin (5-HT) is a neurotransmitter responsible for a wide range of pharmacological reactions. Many gastrointestinal prokinetics such as benzamides (e.g., metoclopramide, cisapride) have binding affinity for 5-HT₄ receptors and the pharmacological effect of these compounds is thought to be based on 5-HT₄ receptor agonism. A set of benzamide derivatives were tested as selective 5-HT₄ receptor agonists. They performed modification of the parent compound 4-amino-5-chloro-2-methoxy-N-[1-(6-oxo-6-phenylhexylpiperidin-4-yl) methyl] benzamide (Scheme 15) which have the ability to enhance both upper and lower gastrointestinal motility without any significant adverse

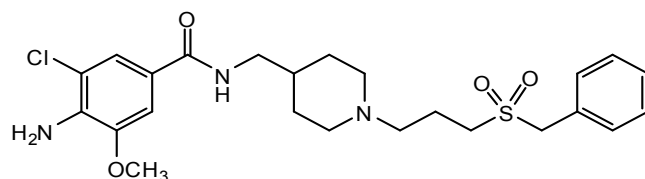
effects [12]. A Series of 4-amino-5-chloro-2-methoxy-N-(piperidin-4-yl-methyl) benzamides with a polar substituent group at the 1-position of the piperidine ring was evaluated for its effect on gastrointestinal motility. The benzoyl, phenylsulfonyl, and benzylsulfonyl derivatives accelerated gastric emptying and increased the frequency of defecation. One of them, 4-amino-N-[1-[3-benzyl sulfonyl]propyl]piperidin-4-yl methyl]-5-chloro-2-methoxy benzamide (Scheme 16), was a selective 5-HT₄ receptor agonist offering potential as a novel prokinetic with reduced side effects derived from 5-HT₃ and dopamine D₇ receptor binding affinity. In the oral route of administration, this compound enhanced gastric emptying and defecation in mice, and has a possibility as a prokinetic agent, which is effective on both the upper and lower gastrointestinal tract [13]. (Azaadamantanone was converted to a series of amino azadamantanone benzamides (Scheme 17a-d) were profiled for serotonin receptor activity. Aminomethyl azadamantane



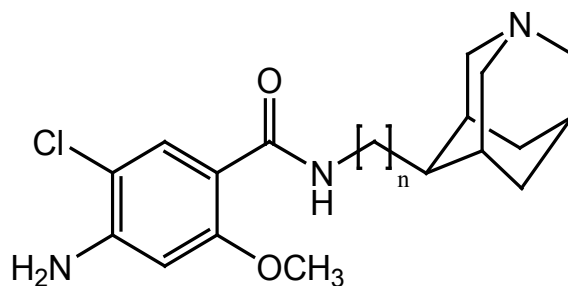
Scheme 14: R₁=2-Phenethyl; R₂,R₃=C₂H₅; X=H.



Scheme 15

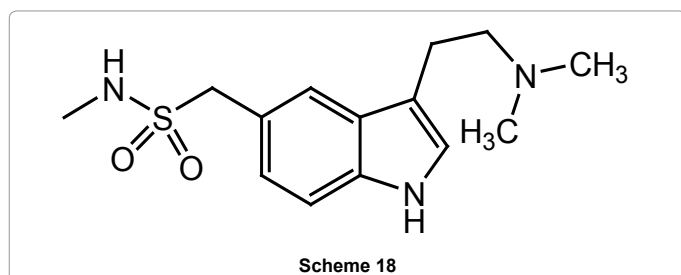
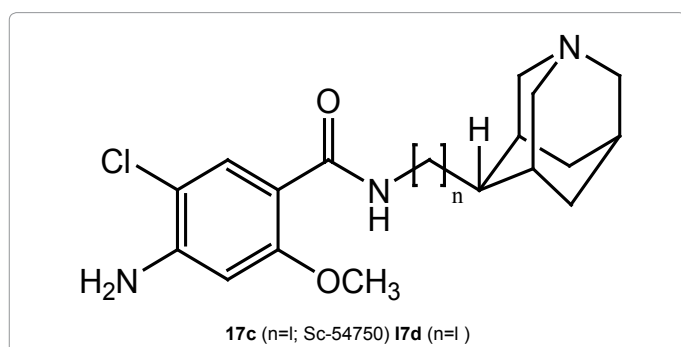
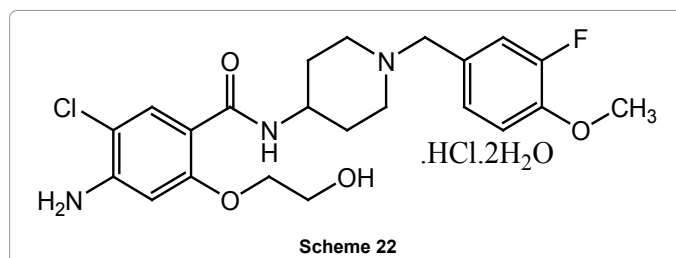
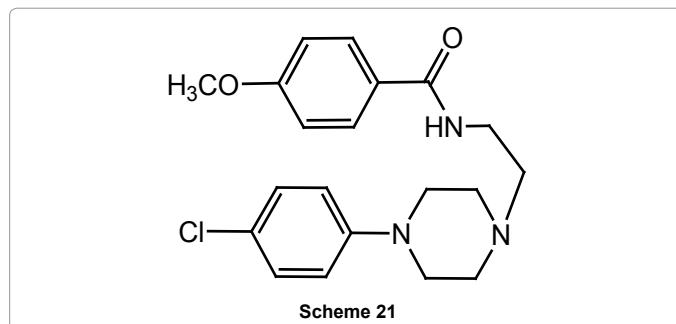
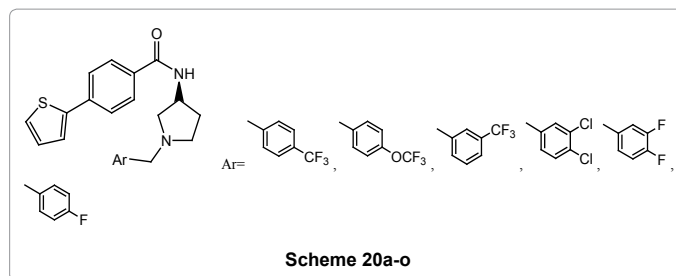
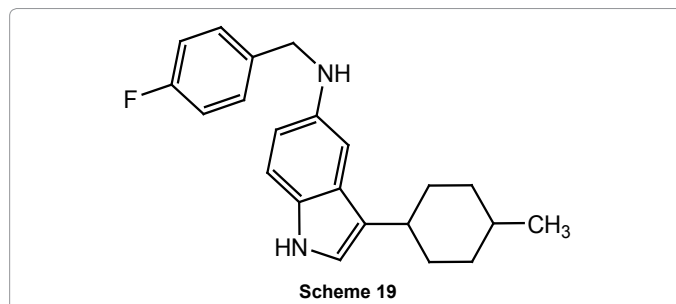


Scheme 16



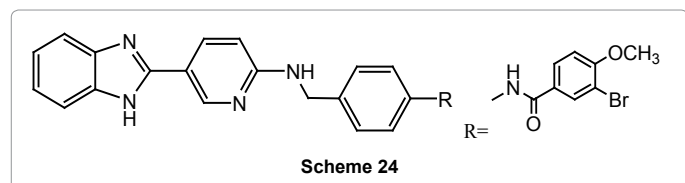
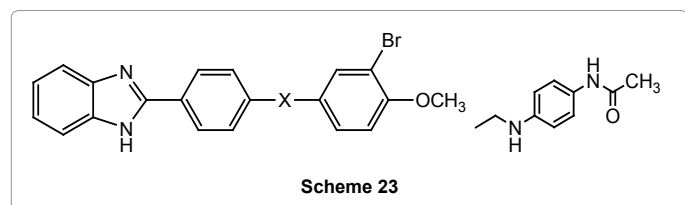
Scheme 17: a (n=0); b (n=0).

SC-54750 is a potent 5-HT₄ agonist and antagonist with *in vivo* efficacy in gastroparesis models and also inhibits cisplatin induced emesis [14]. Several fused bicycle systems have been investigated to serve as the core structure of potent and selective 5-HT_{1F} receptor agonists. Replacement of the indole nucleus in Scheme 18 with indazole and inverted Indazole provided more potent and selective 5-HT_{1F} receptor ligands (Scheme 19). Indoline and 1,2-benzisoxazole systems also provided potent 5-HT_{1F} receptor agonists. The 5-HT_{1A} receptor selectivity of the indoline and 1,2-benzisoxazole-based 5HT_{1F} receptor agonists could be improved with modification of the benzoyl moiety of the benzamides. The combination of D₄ and S-HT_{2A} receptor blockade is attractive for a number of reasons. A favorable 5-HT₂/D₂ ratio may limit the propensity of a compound to induce extrapyramidal symptoms (EPS) (Scheme 20a-o). 5-HT_{2A} antagonists are also known to be efficacious in the treatment of negative symptoms of schizophrenia. In addition, cortical dopaminergic systems are regulated by 5-HT indirectly via glutamatergic and GABAergic systems, suggesting a synergistic relationship between the dopaminergic and serotonergic systems. A series of N-[(3S)-1-benzylpyrrolidin-3-yl]- (2-thienyl) benzamides (Scheme 21) has been found to bind with high affinity to the human D₄(HD₄) and 5-HT_{2A} receptors. Several compounds displayed selectivity for these receptors versus HD₂ and α₁ adrenergic receptors of over 500-fold [15,16]. A series of N- [I-(1-substituted 4-piperidiny)] benzamides were prepared and compounds were tested for their binding to 5-HT₄ receptors and effects on gastrointestinal motility in conscious dogs. 4-Amino-N-[1-(4-aminobutyl)-4-piperidinylniethyl]-4-pipericlinyl]-5-chloro-2-methoxy-benzamide (Scheme 21) was found to have a potent binding affinity for 5-HT₄ receptor (IC₅₀: 6.47mM) and showed excellent prokinetic activity [17]. The KDR-5169, 4-amino-5-chloro-N-[1-(3-fluoro-4-methoxybenzyl) piperidin-4-yl]-2-(2-hydroxy ethoxy) benzamide hydrochloride dehydrate (Scheme 22) is a prokinetic with a dual action i.e., stimulation of the 5-HT₄ receptor and antagonism of the dopamine D₂ receptor. The *in vitro* activities of KDR-5169 towards both receptors and demonstrated the effect of the compound on gastrointestinal motor activity in conscious dogs and rats.



Antitumor activity

A novel class of N-(4-{{4-(1H-benzoimidazol-2-yl) aryl amino} methyl}-phenyl) benzamides and described them as inhibitors of the endo-β-glucuronidase that degrades heparanase. Heparanase, an endo-β-D-glucuronidase that degrades heparin sulfate glycosaminoglycans in the extra cellular matrix (ECM) and the basement membrane, is involved in tumor cell invasion, angiogenesis, and other physiological and pathological processes [18,19]. Among the compounds N-(4-{{4-(1H-benzimidazol-2-yl)phenylamino}-methyl}-phenyl)-3-bromo-4-methoxybenzamide (Scheme 23), and N-(4-{{5-(1H-benzoimidazol-2-yl)-pyridin-2-yl-amino}methyl}-phenyl)-3-bromo-4-methoxybenzamide (Scheme 24) displayed good heparanase inhibitory activity (IC₅₀ 0.23-0.29 μM), with the latter showing oral exposure in mice. Iodobenzamides are reported to possess sonic affinity for melanoma. In order to identify the compound having the most appropriate pharmacokinetic properties as a potential melanoma imaging agent, thirteen new [¹²⁵I] radioiodobenzamides with a butylenes

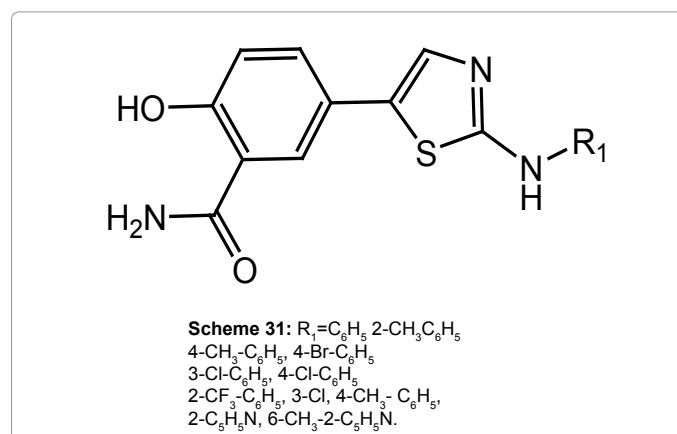
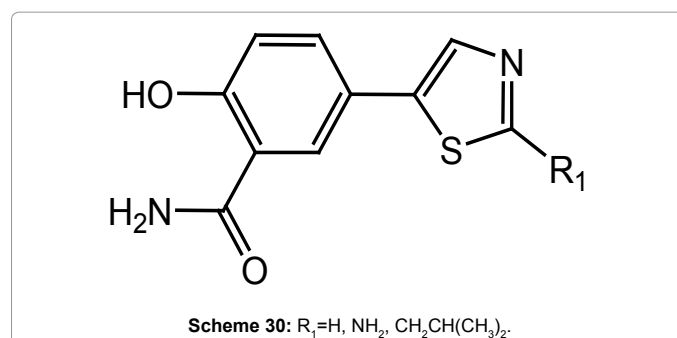
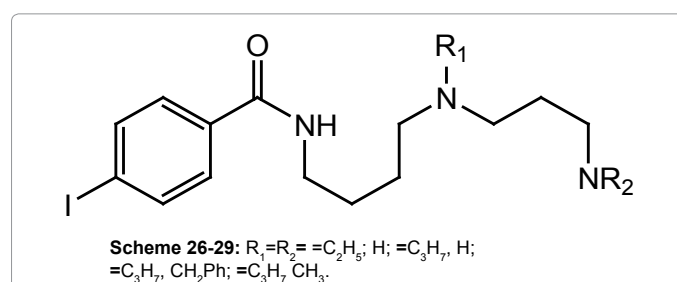
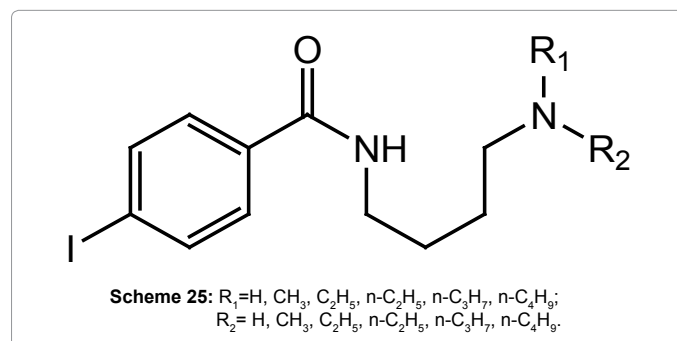


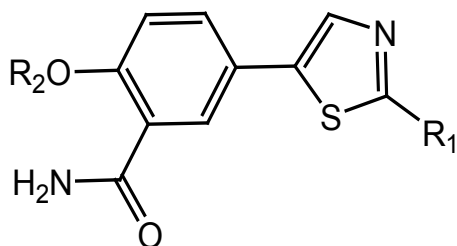
amide-amine spacer and various substituents on the terminal amino group were investigated. The radioiodination and biodistribution in B_{16} melanoma bearing (57BL6 mice are described and compared to [^{125}I] labeled N-(2-diethylaminocetyl)-4-iodoben/amide {[^{125}I] BZA) (Scheme 25), with reference compound changes in the terminal amino constituents induced modifications of lipophilicity, tumor uptake and organ distribution. The dimethyl aminobutyl iodobenzamide appeared to be the most promising radiopharmaceutical imaging agent for the detection of melanoma and its metastases [20]. In the course of investigations aimed at improving the biological characteristic of iodobenzamides for melanoma therapeutic applications, four derivatives containing a spermidine chain have been prepared and radiolabeled with *In vitro* studies showed that all compounds displayed high affinity for melanin superior to the reference compound BZA. *In vivo* biodistribution was investigated in B_{16} melanoma-bearing mice. All four compounds, particularly benzamide, showed accumulation in the tumor, but lower, however than that of BZA. Moreover, high concentrations of radioactivity in the organs, namely, the liver and lungs, demonstrated nonspecific tumoral uptake, in view of these results, compounds (Schemes 26-29) do not appear to be suitable radiopharmaceuticals for melanoma radionuclide therapy [21].

Antimicrobial activity

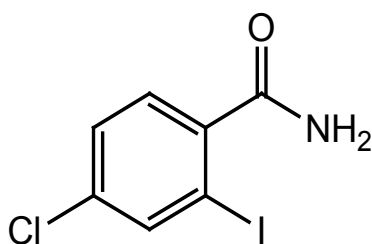
Some 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxybenzamides (Scheme 30), 5-{2-[(N-substituted aryl)amino]-1,3-thiazol-5-yl}-2-hydroxybenzamides (Scheme 31) and their 2-butoxy and 2-propyloxy derivatives (Scheme 32) and their anti-fungal activity. Among the tested compounds, the compound 5-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]-2-butyloxybenzamide emerged as most active compound [22]. The synthesis of some N-(2-hydroxy-4-substituted phenyl) benzamides, phenyl acetamides and furamids as the possible metabolites of benzoxazoles was performed in order to determine their *in vitro* antimicrobial activity against three gram positive bacteria, two gram negative bacteria and the fungus *C. albicans* and their activities were compared with several control drugs. Some compounds were found active at a MIC value of 12.5 $\mu\text{g/ml}$ against the gram-negative microorganism *P. aeruginosa*. Most of the compounds showed antibacterial activity at a MIC value 25 $\mu\text{g/ml}$ against the gram-positive bacteria *S. aureus*. For the antifungal activity against *C. albicans*, one of the compound was found to be more active than the other derivatives. One compound possessed two dilutions better antifungal activity than its cyclic analogue, benzoxazole IV, against *C. albicans* [23]. The N-(1-Phenyl-4-carboxypyrazol-5-yl)-, N-(indazol-3-yl)- and N-(indazol-5-yl)-2-iodobenzamides (Scheme 33), with benodanil-like structure, which were synthesized by refluxing in acetic acid the corresponding benzotriazinones with potassium iodide for 1 h in order to study the role on the antifungal activity of the N-substitution with

an aromatic heterocyclic system on benzamide moiety. Among the tested iododerivatives, some of the compounds possessed interesting activities toward some phytopathogenic fungal strains [24]. Some N-(o-hydroxyphenyl) benzamides and benzacetamides to determine their *in vitro* antimicrobial activity against two gram positive bacteria, three gram negative bacteria and the fungus *C. albicans*. The compounds were compared with several control drugs. The derivative (Scheme 34), 4-amino-N-(o-hydroxyphenyl) benzamide, was found active at an MIC value of 25 $\mu\text{g/ml}$ against the gram negative microorganism *K. pneumoniae*. Most of the compounds exhibited antibacterial activity

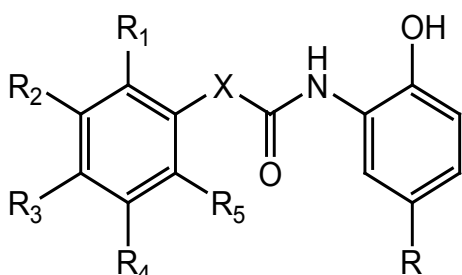




Scheme 32: R₁=CH₃-NH₂, HC₆H₅, NH-4-CH₃-C₆H₅, CH₃, NHC₆H₅, NH-3-Cl-C₆H₅, R₂=Propyl, Butyl.



Scheme 33



Scheme 34: X=CH₃, R₂=H, Cl, CH₃, NO₂, R₁=H, CH₃, OCH₃, R₂=H, OCH₃, R₃=H, Cl, Br, CH₃, NO₂, OCH₃, C(CH₃)₃, F; R₄=H, OCH₃, R₅=H, OCH₃.

at MIC value of 25 µg/ml against *P. aureginosa*. For the antifungal activity against *C. albicans*, compounds (Scheme 34) were found more active than the other derivatives (MIC 12.5 µg/ml). The antimicrobial activity of some of these benzamides and phenyl acetamide derivatives (Scheme 34), possible metabolites of benzoxazoles, was also compared with that of the cyclic analogues. Compound (Scheme 34) possessed two dilutions better antibacterial activity than its cyclic analogue the benzoxazole derivative against *C. albicans*, whereas it was possessing one dilution better antibacterial activity against *S. faecalis* and *K. pneumoniae*.

Antidepressant activity

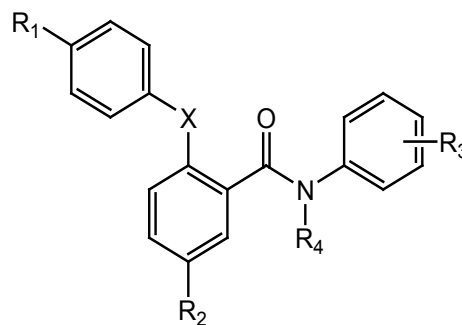
Although a wide assortment of agents is currently available for the treatment of depression, this disorder remains poorly managed in a large proportion of patients. The effects of selective antagonists of the tachykinin NK₁, NK₂ and NK₃ receptors in the forced swim test, a commonly used screen for antidepressants. Rats were given CP-96, 345 (2S,3S)-cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)-methyl]-1-azabicyclo[2.2.2]octan-3-amine, SR 48968 (S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-diclorophenyl)-

butyl) benzamide, or SR 142801 (S)-(N)-(1(3-(1-benzoyl-3-(3,4-dichlorophenyl) piperidin-3-yl) propyl-4-phenylpiperidin-4-yl)-N-methylacetamide antagonists of the NK₁, NK₂ and NK₃ receptors, respectively at doses of 2.5, 5 and 10 mg/kg i.p.,. The time of immobility during the forced swim test was used as an indicator of antidepressant activity of the antagonists. All antagonists had decreased immobility times.

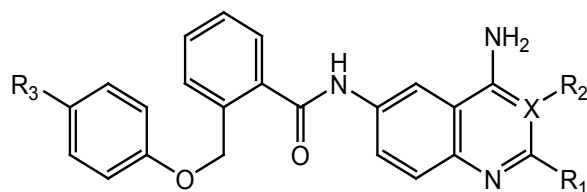
Miscellaneous

K_{ATP} channels are found in different tissues, such as the heart vascular smooth muscle, central neurons and pancreatic β cells. Activators of K_{ATP} channels of smooth muscle (e.g., diazoxide and pinacidil) have been explored as drugs for treatment of cardiovascular diseases. It has been suggested that activators of β cell K_{ATP} channels can be used in the treatment of metabolic diseases through an inhibition of insulin release to induce β cell rest. The 2-(4-methoxyphenoxy)-5-nitro-N-(4-sulfamoylphenyl) benzamides (Schemes 35-43), its close analogues as an activator of Kir6.2/SUR/K_{ATP} channels of β cells and inhibit glucose stimulated insulin release [25-27].

The NOP (ORL₁, OP₄) receptor is a G protein-coupled receptor closely related to the OP₁, OP₂ and OP₃ opioid receptors but having poor affinity with the opioid peptides. The NOP receptor is widely distributed in both central and peripheral nervous system and it is involved in many physiological effects including nociception, attenuation of anxiety, inhibition of learning and memory, stimulation of food intake, diuresis inhibition of reward pathways in drug addiction, inhibition of tachykinergic bronchoconstriction, hypotension, bradycardia, and inhibition of colonic motility. A series of 4-amino-2-methylquinoline and 4-aminoquinazoline derivatives (Scheme 44a-n), including the reference NOP antagonist JTC-801 and their *in vitro* pharmacological properties were investigated. 3-Substitution of the quinoline ring resulted very critical for affinity, so 3-methyl derivative (Scheme 44c) showed a similar potency compared with reference (Scheme 44a) while bulky lipophilic or electron withdrawing groups in the same position

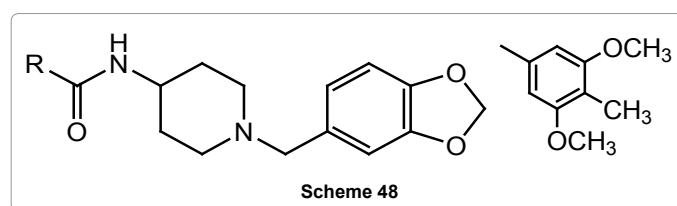


Scheme 35-43: R₁=OCH₃, H, R₂=NO₂, H, NH₂, CN, R₃= 4-SO₂NH₂, 4-OCH₃, 4-F, 4-COCH₃, 3-SO₂NH₂, 2-SO₂, NH₂, 4-Cl, R₄=H, CH₃, CH₂CH₃.

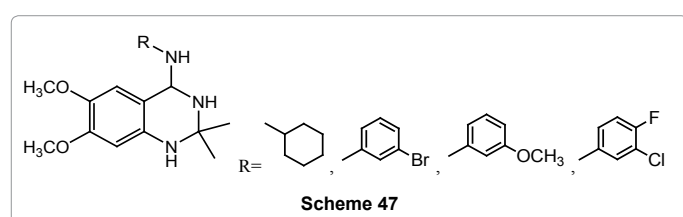
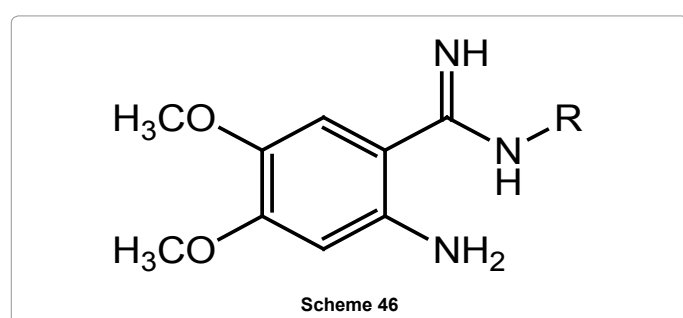
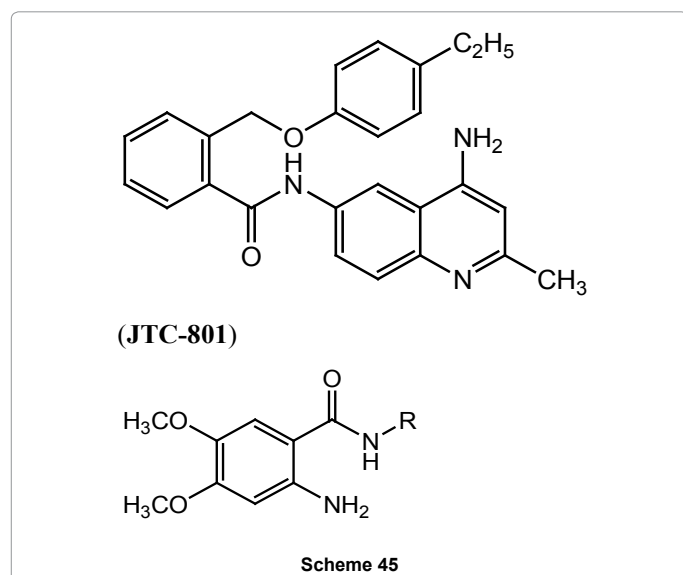


Scheme 44: (a-n) R₁=CH₃, (CH₂)₄, H; R₂= H, C₂H₅, (CH₂)₄, C₆H₅, CO₂C₂H₅; R₃=C₂H₅; X=C, N.

strongly decreased affinity [28]. The epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK) is one of the important kinases that play a fundamental role in signal transduction pathways. EGFR and its ligands (EOF, TGF- α) have been implicated in numerous tumors of epithelial origin and proliferative disorders of the epidermis such as psoriasis. Therefore, the design of inhibitors toward EGFR-PTK is an attractive approach for the development of new therapeutic agents. The benzamides (Scheme 45) and the benzamidines (Scheme 46) as well as the cyclic benzamidines (Scheme 47) were designed as the mimics of 4-anilino quinazolines for an inhibitor of EGFR tyrosine kinase. The specific inhibitions of v-Src kinase were observed in the benzamides, and the benzamidine, whereas the specific inhibitions of v-Src kinase were observed in the benzamide and benzamidine at a 10 $\mu\text{g}/1\text{ml}$ [29]. The continued quest for an orally active MCHr1 antagonist as an effective treatment for obesity, a series of potent benzamide containing MCHr1 antagonists has been identified. The compound with the best combination of MCHr1 binding affinity and functional activity had good oral bioavailability in dog and was evaluated in a DIO mouse model for efficacy. Compound (Scheme 48) demonstrated sustained moderate efficacy when dosed at 30 mpk qd in this chronic model of weight loss [30]. Several potent MCHr1 antagonists based on ortho-

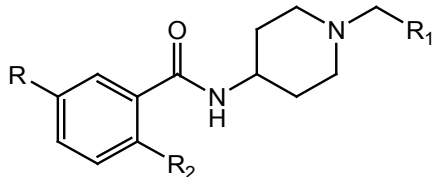


amino benzamide and nicotinamide scaffolds exemplified by Schemes 49 and 50 have been designed and evaluated for the treatment of obesity. Compounds from both these series exhibit dose-dependent sustained efficacy in an obese murine weight loss model [31]. The identified (bis) sulfonic acid, (bis) benzamidcs (Schemes 51-54) as compounds that interact with the follicle stimulating hormone receptor (FSHR) and inhibit FSH-stimulated cAMP accumulation with IC_{50} values in the low micromolar range. The SAR studies using novel-analogues of Schemes 51-54 revealed that two phenylsulfonic acid moieties were necessary for activity and that the C-C double bond of the stilbene sub-series was the optimum spacer connecting these groups [32]. Selected analogues (Schemes 52-54) were also able to block FSHR-dependent estradiol production in rat primary ovarian granulosa cells and progesterone secretion in a clonal mouse adrenal Y_1 cell line. IC_{50} values of these compounds in these assays were in the low micromolar range. Optimization of the benzoic acid side chains of (Schemes 51-54) led to gains in selectivity versus activity at the thyroid stimulating hormone (TSH) and receptor (TSHR). Two benzamide derivatives as dopamine D4 receptor antagonists, YM-50001 (4) and N-[2-[4-(chlorophenyl)piperizin-1-yl]ethyl]-3-methoxybenzamide (Schemes 55 and 56), were labeled by positron-emitter and their pharmacological specificities to dopamine D4 receptors were examined by quantitative autoradiography and position emission tomography (PET) [33]. Various neurokinin receptor antagonists especially dual NK_1/NK_2 antagonists, may represent a treatment option for asthma and other airway diseases, particularly since lung tissue from asthma patients has been shown to over express NK_1 and NK_2 receptors. The N-[(R₁R)-1-(4-Chlorobenzyl)-3-(2-oxoazepan-3-yl)carbonyl]allyl-N-methyl-3,5-bis(trifluoromethyl)benzamide (Schemes 57) DNK 333) exhibiting a 5-fold improved affinity to the NK_2 receptor in comparison to Scheme 58. Simplification of the structure via elimination of a chiral centre led to 3-[N-3,5-bis(trifluoroniethyl)benzoyl-N-(3,4-dichlorobenzyl)-N-methylhydrazino]-iV-[R-2-oxo-azepan-3-yl] propionamide a potent and fairly balanced NK_1/NK_2 antagonist. The (\pm)-N-[5-(Diethylamino)-1-phenylpentyl]-4-nitrobenzamide hydrochloride (Scheme 59) is known as the representative of new class III antiarrhythmic drugs which are highly effective and well tolerated in patients with atrial flutter and fibrillation or supraventricular tachycardia. A series of 1,5-diaminopentane derivatives, structurally related to nibentan, was tested for antifibrillatory activity. Some of the compounds were found to be more potent than nibentan and possessed a longer duration of action. The antifibrillatory activity of (\pm)-N-[5-(diethylamino)-1-(4-methoxyphenyl) pentyl]-4-nitrobenzamide hydrochloride was comparable to that of nibentan but exceeded the potency of D-sotalol and sematilide [34,35].

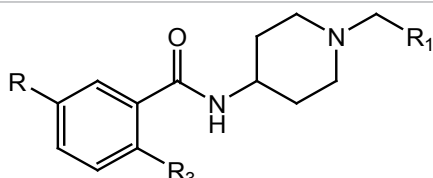


Discussion

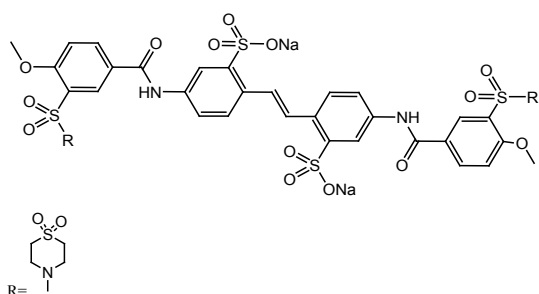
Several biological activities studied by different researchers in organic scaffolds are based on the benzamide systems. The effects of substitutions on benzamide either by aliphatic, aromatic or heteroaromatic systems are leading to various types of biological activities. Few benzamide congeners were screened out as the most effective molecules delivering immense activity in each of the target



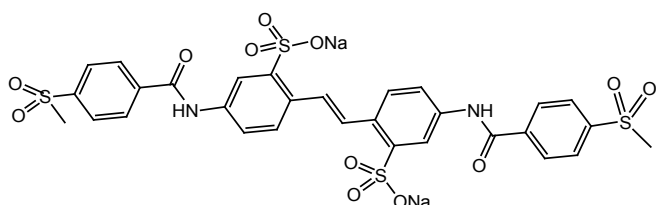
Scheme 49: R=Cl R₁=



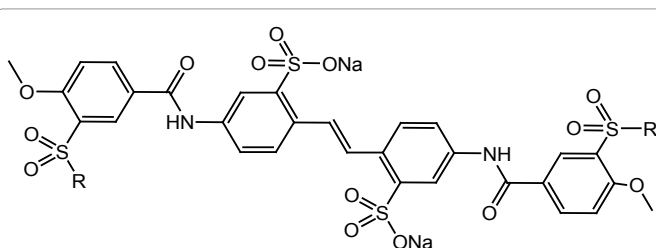
Scheme 50: R₂= R₃=



Scheme 51



Scheme 52



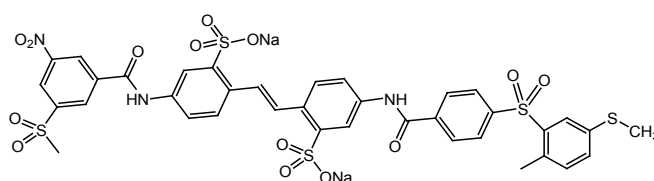
Scheme 53

studies. Upon varying or substituting electron-withdrawing or electron-releasing functional groups directly to the nitrogen atom of benzamide or on the phenyl/benzyl ring attached to the benzamide, the respective biological action was found to vary in almost all cases. After careful study of numerous examples in terms of targeted molecular designs, one may have the idea to structure further classes of featured molecules, leading to an innovative drug discovery. The various substitutions were chosen in order to identify the possible structure-activity relationships. Various compounds synthesized in this way are subjected to screen

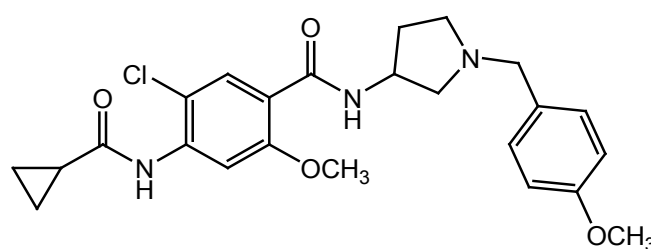
for their biological activity. The benzamide template contains some building features and pharmacological points that provides a wide range of different biological targets in medicinal chemistry. Benzamide analogues have been a great interest of biological activities that can be found across number of different therapeutic areas.

Conclusion

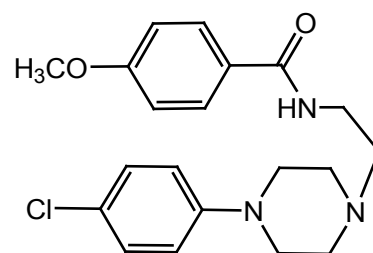
In conclusion, benzamide derivatives were synthesized by different methods and evaluated as different types of biologically active agents. The Substituted benzamides will be consider as bioactive compounds and may be treated as medicinal material. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.



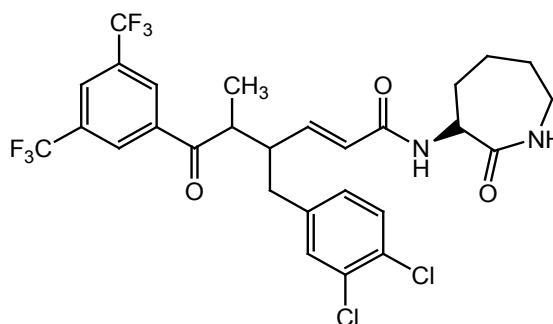
Scheme 54



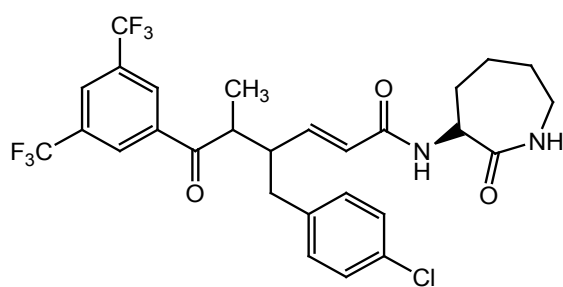
Scheme 55



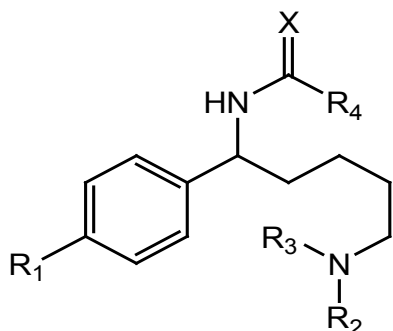
Scheme 56



Scheme 57



Scheme 58



Scheme 59: R₁=H, CH₃O, NO₂, R₂=C₂H₅, CH₃; R₃=C₂H₅, (CH₂)₂C₆H₃(OCH₃), 3,4 -CH₂Ph; R₄=4-NO₂C₆H₄, 3-NO₂C₆H₄, 3-Pyridyl, Ph, 4-COOC₂H₅C₆H₄, 4-SO₂CH₃C₆H₄, 4-OHC₆H₄, 4-NO₂C₆H₄, PhC₆H₄CONH₂; X=O, NH.

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