Bioorganic & Medicinal Chemistry Letters 24 (2014) 495–500

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Microwave assisted synthesis of naphthopyrans catalysed by silica supported fluoroboric acid as a new class of non purine xanthine oxidase inhibitors

Sahil Sharma [a], Kirti Sharma [a], Ritu Ojha [a], Dinesh Kumar [a], Gagandip Singh [b], Kunal Nepali [a,*], P. M. S. Bedi [a,c,*]

[a] *Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143005, Punjab, India*
[b] *Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, Punjab, India*
[c] *Sri Sai College of Pharmacy, Badhani, Pathankot 145001, Punjab, India*

ARTICLE INFO

Article history:
Received 4 September 2013
Revised 27 November 2013
Accepted 10 December 2013
Available online 16 December 2013

Keywords:
Xanthine oxidase
Naphthopyrans
Fluoroboric acid
Silica
Microwave

ABSTRACT

A series of naphthopyrans was synthesized employing silica supported fluoroboric acid under solvent free conditions in a microwave reactor. The catalytic influence of HBF_4–SiO_2 was investigated in detail to optimize the reaction conditions. The synthesised compounds were evaluated for in vitro xanthine oxidase inhibitory activity for the first time. Structure–activity relationship analyses have also been presented. Among the synthesised compounds, NP-17, NP-19, NP-20, NP-23, NP-24, NP-25 and NP-26 were the active inhibitors with an IC_{50} ranging from 4 to 17 μM. Compound NP-19 with a thiophenyl ring at position 1 emerged as the most potent xanthine oxidase inhibitor (IC_{50} = 4 μM) in comparison to allopurinol (IC_{50} = 11.10 μM) and febuxostat (IC_{50} = 0.025 μM). The basis of significant inhibition of xanthine oxidase by NP-19 was rationalized by its molecular docking at MTE binding site of xanthine oxidase.

Xanthine oxidase, a molybdoflavoprotein catalyses the oxidative hydroxylation of hypoxanthine and xanthine to produce uric acid and reduction of oxygen at the flavin centre generating reactive oxygen species either as superoxide anion radical or hydrogen peroxide.[1–3] Catalysis by xanthine oxidase to produce uric acid and reactive oxygen species leads to many diseases like gout and at least symptoms of diseases like oxidative damage to the tissue.[2] Despite the potential of purine base compounds as xanthine oxidase inhibitors such as allopurinol,[3,4] 2-alkyl hypoxanthines,[5] pterin and 6-formylpterin,[6] there is a continuous search for non-purine based xanthine oxidase inhibitors. The revived interest among the researchers towards the xanthine oxidase inhibitors with structurally diverse and non-purine isosters[7] such as feboxustat,[8] flavonoids,[9] FYX-051,[10] 1,3-diaryltriazole derivative[11] and curcumin[12] can be attributed to the interactions of purine analogs xanthine oxidase inhibitors on activities of purine and pyrimidine metabolizing enzymes leading to Steven Johnson syndrome and worsening of renal function induced in some of the patients.[2–4]

Recently our research group reported *N*-(1,3-diaryl-3-oxopropyl)amides[13] (**1**), *N*-acetyl pyrazolines[14] (**2**) and azaflavones[15] (**3**) (Fig. 1) as non purine based xanthine oxidase inhibitors.

In continuation of our search for non-purine based xanthine oxidase inhibitors, the present study investigates the potential of naphthopyrans as a new class of non purine xanthine oxidase inhibitors in view of the potent xanthine oxidase inhibitory potential of some phytoconstituents possessing benzopyran nucleus such as Apigenin and Esculetin (Fig. 2) which are ideal molecules to represent their respective classes of compounds.

Structure–activity relationship established for Apigenin and Esculetin reveals that the presence of hydroxyl groups at specific positions on the benzopyran nucleus (Ring A) is an important structural feature for the inhibitory potential. The present study explores the role of naphthyl moiety as a surrogate for the hydroxy

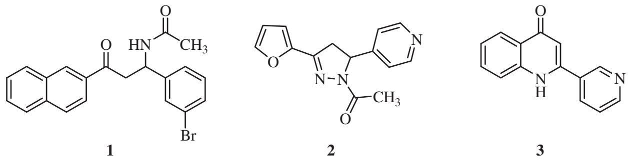


Figure 1. Structures of non purine xanthine oxidase inhibitors.

---

* Corresponding authors at present address: Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab 143005, India. Tel.: +91 8146096564 (K.Nepali).

E-mail addresses: kunal_8855@rediffmail.com (K. Nepali), bedi_preet@yahoo.com (P.M.S. Bedi).

0960-894X/$ - see front matter
http://dx.doi.org/10.1016/j.bmcl.2013.12.031

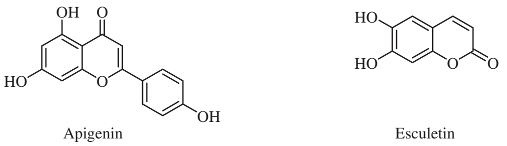


Figure 2. Structures of Apigenin and Esculetin.

substituted fused benzene ring in benzopyrans. The placement of the naphthyl ring was speculated to enhance the arene–arene interaction in addition to hydrophobic interactions after observing the structural topology of the receptors active site. However this replacement will result in loss of hydrogen bonding interaction

With this background, a series of naphthopyrans was designed, synthesised and evaluated for xanthine oxidase inhibition. Literature survey revealed that a convenient synthetic protocol is still lacking for this class of compounds. Multicomponent synthesis by lewis acids/bronsted acids have gained enough attention in the recent past.[17] Moreover, bronsted acids adsorbed on silica have been reported to be excellent heterogenous catalysts.[18] With our continuous investigation on developing efficient methodology for the synthesis of non purine xanthine oxidase inhibitors[13] and influenced by the tight legislation on maintenance of greenness in synthetic pathways and processes,[16] that is, to prevent generation of waste, avoid use of auxiliary substances (e.g., solvents, additional reagents) and minimise energy requirements, we report herein, for the first time, three-component cyclocondensation of an aldehyde, β-naphthol and active methylene comppunds, accomplished by using silicated fluoroboric acid as catalyst under solvent-free condition and microwave (MW) irradiation, which appears to be an efficient and environmentally friendly preparation of the target compounds. Adsorption of reagents on to insoluble inorganic/organic support improves activity and selectivity of reagent by increasing effective surface area of reagent dispersed on support up to hundred times.

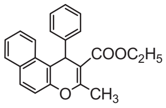
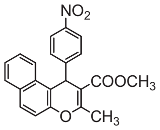
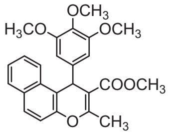
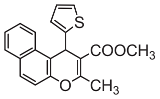
In an attempt to investigate the catalytic efficiency of various Bronsted acids adsorbed on silica (BA–silica) (Table 1), a model reaction was performed for the synthesis of target compound (Scheme 1).

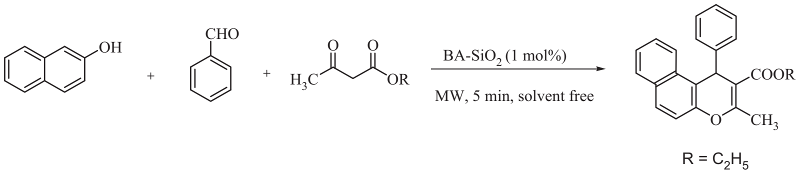
Table 1 reveals that Fluoroboric acid adsorbed on silica most efficiently catalysed the synthesis of the target compound. The high catalytic influence of HBF_4–SiO_2 could be attributed to the fact that HBF_4 is weak protic acid which when adsorbed on silica might have circumvent the problem of side reactions whereas in case of strong bronsted acids such as perchloric aicd, sulphuric acid and nitric acid, the yields were not that high. Silica was also employed as an activator to evaluate its activating power. However the reaction did not proceed as desired indicating that the role of silica was just limited as an adsorbent.

Table 1
Percentage yield of naphthopyran with various activators

Entry	Activator (BA–SiO_2)	% age yield
1	HNO_3–SiO_2	43
2	H_2SO_4–SiO_2	52
3	$HClO_4$–SiO_2	49
4	HBF_4–SiO_2	65
5	SiO_2	–

Table 2
Percentage yield with varying mol % of the catalyst and time of exposure to microwave irradiation of some selected naphthopyrans. The bold values indicates the most appropriate conditions

Structure	Loading (mole %)	Time (min)	Yield (% age)
	1	5	65
		10	69
		15	67
	5	5	75
		10	**89**
		15	81
	10	5	69
		10	79
		15	71
	1	5	69
		10	79
		15	73
	5	5	79
		10	**92**
		15	89
	10	5	72
		10	83
		15	76
	1	5	66
		10	73
		15	69
	5	5	75
		10	**83**
		15	78
	10	5	69
		10	77
		15	73
	1	5	53
		10	61
		15	58
	5	5	63
		10	**76**
		15	69
	10	5	58
		10	68
		15	63



Scheme 1. Synthesis of naphthopyrans.