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Synthesis of 4-hydroxy-1-methylindole and benzo[*b*]thiophen-4-ol based unnatural flavonoids as new class of antimicrobial agents☆

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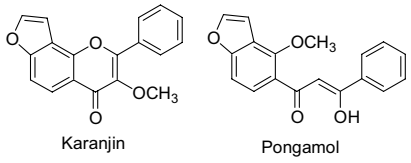
Abstract—Synthesis of nitrogen and sulfur heterocyclic mimics of furanoflavonoids have been achieved for the first time. Synthesized flavonoid alkaloids and thiophenyl flavonoids have been screened for antifungal and antibacterial activities. All the test compounds barring **25** exhibited antifungal activity. The compound **19** was the best and showed comparable MICs to the known compound karanjin. Compounds **5**, **12**, **14** and **22** also showed comparable MIC to karanjin.

1. Introduction

The clinical relevance of fungal diseases has increased enormously in the second half of the 20th century, mainly because of an increasing population of immunocompromised hosts, including individuals infected with HIV, transplant recipients and patients with cancer.[1,2] The fungal threat will continue to increase, as shown by the occurrence of aspergillosis in severe acute respiratory syndrome (SARS)[3] and by the inclusion of *Coccidioides immitis* as a potent agent of bioterrorism.[4] The crude mortality from opportunistic fungal infections still exceeds 50% in most human studies and has been reported to be as high as 95% in a bone marrow transplant recipients infected with *Aspergillus* spp.[5]

During our continuing efforts to identify antifungal leads from plant sources we have isolated furanoflavonoids from *Pongamia pinnata* fruits.[6,7] These compounds possess various kind of biological activities.[8] Among the compounds isolated by us most prominent were karanjin, and pongamol. Karanjin has been reported to be hypoglycemic,[9] antifungal,[10] synergist to insecticides, antifeedent[11] and pongamol has antimicrobial[12] activity and is used commercially in cosmetic and sun-screen preparations.[13]



The adequate treatment of mycotic infections is difficult since fungi are eukaryotic organisms with a structure and metabolism that is similar to those of eukaryotic host. For this reason, there is a need to design new compounds with good antifungal activity.

Therefore, in order to explore the potential of furanoflavonoid nucleus as antifungal and antibacterial agents we have devised an easy and efficient methodology to introduce novel pyrrole and thiophene anellated mimics to furanoflavonoids as their heterocyclic counterparts.

2. Results and discussion

2.1. Retrosynthetic scheme

Various methods in the literature regarding synthesis of furanoflavonoids reveal that these compounds can be synthesized from degradation product of furanoflavonoids,

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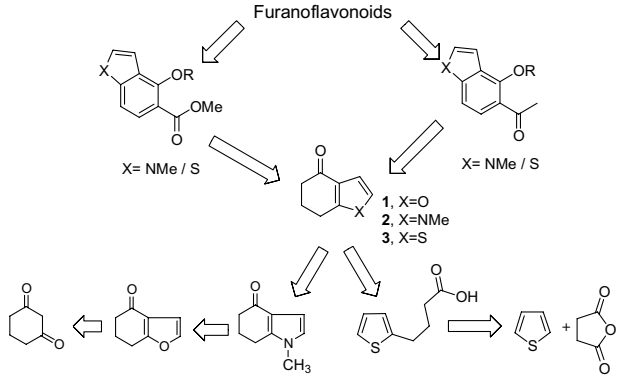
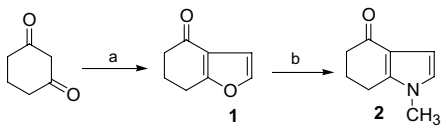
that is, karanjic acid or total synthesis can be achieved starting from cyclohexane-1,3-dione involving multisteps leading to furanoflavonoids.[14] These methods cannot be applied as such to the nitrogen and sulfur heterocyclic mimics of furanoflavonoids. Nitrogen can be inserted to the 4-oxo-4,5,6,7-tetrahydrobenzofuran (**1**) through ammonolysis whereas sulfur heterocyclic mimics can not be generated from **1** as they lack any possible step where sulfur can be inserted to the benzofuranoid nucleus. Corresponding sulfur motif 6,7-dihydro-5*H*-benzo[*b*]thiophen-4-one (**3**) can be generated from thiophene and succinic anhydride as depicted in the retrosynthetic scheme. There is no literature report for synthesis of these key intermediates as well as the final compounds.



2.2. Chemistry

We initiated our studies by preparing starting 4-oxo-4,5,6,7-tetrahydrobenzofuran (**1**). Easy and efficient methods are available for synthesis of 2-substituted-tetrahydrobenzofurans, but these methods can only be applied for synthesis of 2,3-dihydro-2-substituted-tetrahydrobenzofurans due to their limitations.[15,16] Recent studies have shown use of rhodium acetate in dipolar cycloaddition of diazacyclohexane-1,3-diones with vinyl acetates followed by acid catalyzed dehydration to produce **1** in 41–71% yield.[17] Our attempt to synthesize **1**, commenced from commercially available cyclohexane-1,3-dione as shown in Scheme 1. Aqueous solution of cyclohexane-1,3-dione was stirred with bromoacetaldehyde in presence of catalytic amount of TBAI and pH 6–7 was maintained by addition of sodium bicarbonate. After 6 h the reaction mixture was subjected to acid catalyzed dehydration to afford **1** in 78% yield.[18] The synthesis of key intermediate **2** (Scheme 1) was achieved in quantitative yields by ammonolysis of tetrahydrobenzofuran (**1**) with methyl amine in aqueous ethanol contained in a sealed tube at 150 °C for 14 h.[19]



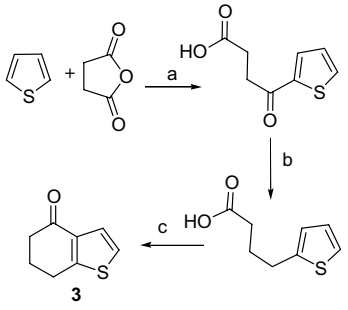
Scheme 1. Reagents and conditions: (a) $BrCH_2CHO$, $NaHCO_3$, H_2O, rt, 6 h (78%); (b) ammonolysis with $MeNH_2$, EtOH in sealed tube, 150 °C, 14 h (90%).

As depicted in the retrosynthetic scheme, sulfur can be inserted to the key intermediate while starting our strategy from thiophene. Friedel–Crafts acylation of thiophene with succinic anhydride catalyzed by Lewis acid $AlCl_3$ and subsequent reduction of carbonyl group by Clemmensen reduction, thereafter conversion of free acid to acid chloride and again Friedel–Crafts acylation afforded **3** in 64% overall yield as shown in Scheme 2.[20]

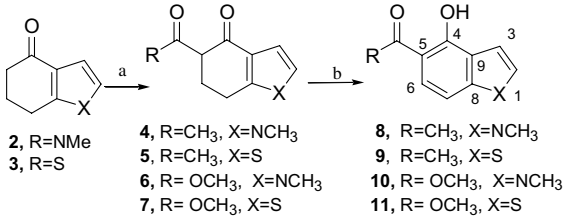
Enolate of **2/3** was generated with NaH and catalytic amount of KH followed by coupling with ethyl acetate and dimethyl carbonate in refluxing DME produced **4**–**7** (80–94%). Compound **4** and **5** existed as keto-enol tautomers (9:1), as indicated from ^1H NMR spectra. Thereafter, DDQ mediated dehydrogenation of **4**–**7** in refluxing dioxane, afforded **8**–**11** (64–85%) (Scheme 3).[14] Compound **16** and **17** were prepared in quantitative yield by methylation of the phenols **10** and **11** with methyl iodide and K_2CO_3 in acetone (Scheme 5).

The synthesis of corresponding chalcones **12**–**15** were achieved in good yield by subjecting intermediates **8/9** to Claisen–Schmidt condensation with substituted benzaldehydes in presence of barium hydroxide in ethanol (Scheme 4).

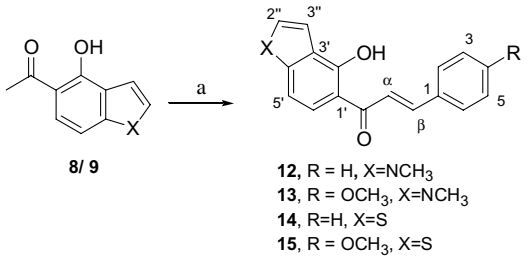
Propanedione analogue (**18/19**) were prepared in (35–40%) yield by condensation of methyl ether **16/17** with acetophenone in the presence of sodium amide in dry



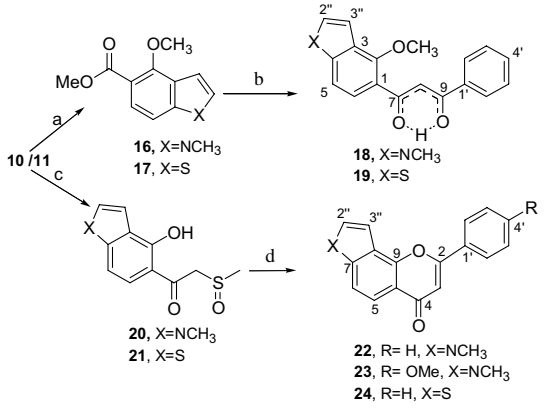
Scheme 2. Reagents and conditions: (a) $AlCl_3$, nitrobenzene, 0–5 °C; (b) Zn–Hg, HCl; (c) $SnCl_4$, CS_2, 0 °C.



Scheme 3. Reagents and conditions: (a) NaH (KH), EtOAc (for **4** and **5**)/dimethyl carbonate (for **6** and **7**), DME, reflux, 4 h; (b) DDQ, dioxane, reflux, 2 h.



Scheme 4. Reagents and conditions: (a) barium hydroxide, pR-PhCHO, EtOH, reflux, 3 h.



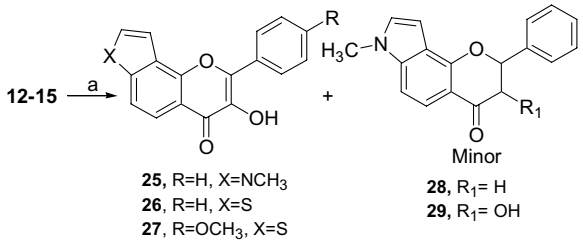
Scheme 5. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 2 h; (b) $NaNH_2$, dry ether, acetophenone, 3 h; (c) NaH, DMSO, dry benzene, 80 °C; (d) piperidine, dry toluene, pR-PhCHO, first at 40 °C, 2 h then at 110 °C, 1 h.

ether (Scheme 5). Reaction was tried with different bases (NaH, KH, ^{t}BuOK) and solvents (THF, DME) but no improvement in yield was observed. Further esters **10/11** were treated with dimsyl anion in DMSO to form the β-ketosulfoxide **20/21** (Scheme 5), which on treatment with benzaldehydes and piperidine in dry toluene first at 40 °C for 2 h, then at 110 °C for 1 h, produced corresponding flavone analogues **22**–**24** (65–76%).[14]

Synthesis of corresponding flavonols were achieved by Algar–Flynn–Oyamada reaction (AFO)[21] of chalcones **12**–**15**. Reaction of sulfur heterocyclic chalcones (**14** and **15**) were neat and produced flavonol **25** and **26** in good yields, whereas, AFO reaction of nitrogen anlogue (**12**) was not efficient and chromatographic purification of products revealed formation of flavonol analogue **25** (30%) as major product along with two minor products flavanone **28** (3%) and flavanonol **29** (5%) (Scheme 6), whereas with chalcone **13** reaction resulted in complex mixture of products.

2.3. In vitro antifungal and antibacterial activity

The minimum inhibitory concentration (MIC) of each compound was determined against test isolates using broth micro-dilution technique as described by the NCCLS.[22,23] MIC of standard antifungal (fluconazole) and the compounds were determined in 96-well tissue



Scheme 6. Reagents and conditions: (a) 8% H_2O_2, 10% KOH, 0 °C, 3 h.

culture plates using RPMI 1640 media buffered with MOPS (3-[*N*-morpholino]propanesulfonic acid) (Sigma Chemical Co.). All the test compounds barring **25** exhibited antifungal activity. The compound **19** was the best and showed comparable MICs to the known compound karanjin. This compound showed activity of 6.25 μg/mL as compared to standard antifungal drug fluconazole, having MIC of 2 μg/mL against *Trichophyton mentagrophytes*. Against each test isolate including bacteria, compound **19** showed good activity whereas the compound **22** exhibited good activity against fungal isolates only. On the contrary compound **12** showed mild activity against bacteria and fungi. Most of the compounds have shown good antifungal activity against *Trichophyton mentagrophytes* but compound **19**, **22** and **12** exhibited good activity against each fungal isolate. It can be inferred from the activity results that substitution by sulfur has produced better results as compared to the nitrogen analogues as revealed from activities of chalcones **12**–**15**, propanediones (**18/19**) and flavonols **25**–**27,** whereas nitrogen analogue for flavone **22** was more active then its sulfur counterpart **24**. Methoxy substituted analogues for all these compounds in general have shown decrease in activity. Two of the compounds **12** and **19** also had some antibacterial activity (Table 1).

3. Conclusion

In conclusion we have accomplished synthesis of novel pyrrole and thiophene anellated flavonoid analogues of furanoflavonoids, all the final compounds including intermediates **4**–**11** are new and synthesized for the first time. Synthesized compounds were evaluated for antifungal and antibacterial activities. Biological studies of heterocyclic analogues of these compounds have revealed that substitution of the heterocyclic oxygen by sulfur has produced marked increase in the antifungal activity, as indicated by activity profile of the compound **19**. Compounds **5**, **12**, **14** and **22** also showed comparable MIC to karanjin.

4. Experimental

4.1. General

Melting points (mp) were taken in open capillaries on an electrically heated melting point apparatus Complab and are uncorrected. IR spectra were recorded on a

Table 1. Antimicrobial activity of heterocyclic analogues

Compound	Minimum inhibitory concentration (MIC) μg/mL against										
	Bacteria					Fungi					
	1	2	3	4	5	6	7	8	9	10	11
4	50	—	—	—	—	50	50	25	25	—	50
5	25	—	—	—	—	25	25	25	12.5	—	25
7	—	—	50	—	50	50	50	25	25	—	50
9	—	—	—	—	—	50	50	50	25	—	50
10	—	—	—	—	—	—	50	50	—	—	—
12	50	25	50	25	25	25	25	25	6.25	—	25
13	—	25	—	25	—	—	25	25	25	50	50
14	50	—	—	—	—	25	25	12.5	12.5	—	25
15	—	—		—	—	—	—	—	25	—	—
18	—	—	—	—	—	25	25	50	25	—	25
19	25	50	25	—	50	12.5	6.25	6.25	6.25	—	25
22	—	—	—	—	—	25	12.5	25	12.5	—	12.5
23	—	—	—	—	—	—	50	—	25	—	—
24	—	25	—	—	—	—	25	—	50	—	—
25	—	—	—	—	—	—	—	—	—	—	—
26	—	—	—	—	—	—	25	25	25	—	—
27	—	—	—	—	—	—	50	—	—	—	—
Karanjin	12.5	12.5	—	12.5	—	12.5	12.5	25	6.25	—	12.5
Pongamol	—	—	—	—	—	—	—	50	12.5	—	—
flu*	ND	ND	ND	ND	ND	0.5	1.0	1.0	2.0	2.0	1.0

(1) *Streptococcus faecalis*, (2) *Klebsiella pneumoniae*, (3) *Escherichia coli*, (4) *Pseudomonas aeruginosa*, (5) *Staphylococcus aureus*, (6) *Candida albicans*, (7) *Cryptococcus neoformans*, (8) *Sporothrix schenckii*, (9) *Trichophyton mentagrophytes*, (10) *Aspergillus fumigatus*, (11) *Candida parapsilosis* (ATCC 22019), flu* = Fluconazole, ND = Not done.

Perkin–Elmer RX-1 spectrophotometer using either KBr pallets or in neat. The FAB-MS were recorded using a beam of Argon (2–8 eV) on Jeol SX 102/DA-6000 mass spectrometer. The NMR spectra were run on an AVANCE DPX 200 and Bruker DRX 300 FTNMR spectrometers. The chemical shifts are reported in δ (ppm) downfield from TMS, which was used as internal standard. Elemental analyses were obtained in a Carlo-Erba-1108 CHN elemental analyzer. Silica gel (60–120 mesh) was used for column chromatography while silica gel (230–400 mesh) was used for flash chromatography. TLC was run either on precoated silica gel 60F254 and RP-18 F254 (Merck) or hand made plates. Detection of spots was done either by iodine vapour, spraying with 1% cerric sulfate in 1 M H_2SO_4 followed by heating at 110 °C, or spraying with 10% methanolic sulfuric acid followed by heating at 110 °C.

4.2. 5-Acetyl-1-methyl-4-oxo-4,5,6,7-tetrahydroindole (4)

To the stirred solution of sodium hydride (1.20 g, 50 mmol) and potassium hydride (100 mg, 2.5 mmol) in dry DME (10 mL) added a solution of **2** (750 mg, 5.0 mmol) in dry DME (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min and then ethyl acetate (2.40 mL, 25 mmol) was slowly added over 10 min. The ice bath was removed and the reaction mixture was heated to reflux for 2.30 h. Reaction mixture was quenched by dropwise addition of ice cold ammonium chloride solution (5 mL) and then poured over aqueous ammonium chloride solution (30 mL), extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by chromatography over silica gel (60–120 mesh), by isocratic elution with chloroform: ethyl acetate (95:05) to afford 824 mg (84% yield) of **4**; viscous, IR (KBr) ν_{max}: 3452, 2944, 1709, 1636, 1514, 1473, 1413, 1354, 1257, 1167, 1080, 754, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 16.17 (OH-chelated), 6.53 (1H, br s, H-2), 6.51(1H, br s, H-3), 3.53 (3H, s, NCH_3), 3.50 (1H, br dd, H-5), 2.47–2.95 (4H, m, H-6, H-7), 2.28 (3H, s, $CO\mathit{CH}_3$); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 206.2 (C-10), 189.6 (C-4), 186.5 (C-10-enol), 176.1 (C-4-enol), 144.2 (C-8), 142.0 (C-8-enol), 124.1 (C-2), 124.0 (C-2-enol), 120.2 (C-9), 106.1 (C-3), 105.9 (C-3-enol), 103.3 (C-5-enol), 60.6 (C-5), 33.8 (NCH_3), 30.0 ($CO\mathit{CH}_3$), 25.6 (C-6), 24.0 (C-6-enol), 27.1 (C-7-enol), 20.4 ($CO\mathit{CH}_3$-enol), 20.0 (C-7); FAB-MS (+ve): 192 $[M+H]^+$, 383 $[2M+H]^+$.

4.3. 5-Acetyl-6,7-dihydro-5*H*-benzo[*b*]thiophen-4-one (5)

The procedure for the synthesis of **4** was repeated (see Section 4.2) with **3** (2.00 g, 0.013 mol) and ethyl acetate (7.60 mL, 0.073 mol), afforded **5**; 2.00 g, (80%); colourless needles, mp 80–81 °C; IR (KBr) ν_{max}: 3530, 2982, 1748, 1719, 1667, 1605, 1429, 1365, 1271, 11154, 1039, 908, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 16.14 (1H, s, OH-chelated-enol form), 7.38 (1H, d, $J = 5.2$ Hz, H-2-enol), 7.37 (1H, d, $J = 5.3$ Hz, H-2-keto), 7.09 (1H, d, $J = 5.1$ Hz, H-3-enol), 7.07 (1H, d, $J = 5.2$ Hz, H-3-keto), 3.61 (1H, t, $J = 7.8$ Hz, H-5-keto), 3.01–3.29 (2H, m, H-7-keto), 2.94–3.0 (2H, m, H-6-enol), 2.67–2.77 (2H, m, H-7-enol), 2.23–2.61 (2H, m, H-6-keto), 2.31 (3H, s, $CO\mathit{CH}_3$-keto), 2.14 (3H, s, $CO\mathit{CH}_3$-enol); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 205.3, (C-10-keto), 189.4 (C-4-keto), 182.9 (C-4-enol),

182.4 (C-10-enol), 156.9 (C-8-keto), 151.9 (C-8-enol), 136.6 (C-9-keto), 136.1 (C-9-enol), 125.3 (C-2-keto), 125.07 (C-2-enol), 124.0 (C-3-keto), 123.7 (C-3-enol), 104.0 (C-5-enol), 66.6 (C-5-keto), 30.5 (C–CO*CH*$_3$-enol), 26.8 (C-6-keto), 24.7 (C-6-enol), 24.6 (C-7-enol), 23.9 (C-7-keto), 21.5 (CO*CH*$_3$-keto); FAB-MS (pos.): *m*/*z* 195 $[M+H]^+$ *m*/*z* 389 $[2M+H]^+$.

4.4. 1-Methyl-4-oxo-4,5,6,7-tetrahydroindole-5-carboxylic acid methyl ester (6)

The procedure for the synthesis of **4** was repeated (see Section 4.2) with **2** (1.00 g, 6.7 mmol) and dimethyl carbonate (3.00 g, 33.5 mmol), afforded **6**; 1.30 g (94%); brown crystals, mp 93–94 °C; IR (KBr) ν_{max}: 2950, 2912, 1733, 1649, 1512, 1465, 1362, 1309, 1219, 1167, 1079, 729, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.66 (2H, br s, H-2, H-3), 3.86 (3H, s, OCH_3), 3.68 (3H, s, NCH_3), 3.58 (1H, dd, J = 8.1, 4.8 Hz, H-5), 3.05 (1H, td, J = 16.5, 6.0 Hz, H-7a), 2.84 (1H, td, J = 16.8, 6.6 Hz, H-7b), 2.66 (1H, m, H-6a) 2.45 (1H, m, H-6b); FAB-MS (pos.): *m*/*z* 208 $[M+H]^+$, 415 $[2M+H]^+$.

4.5. 4-Oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophene-5-carboxylic acid methyl ester (7)

The procedure for the synthesis of **4** was repeated (see Section 4.2) with **3** (2.00 g, 0.013 mol) and dimethyl carbonate (6.55 mL, 0.073 mol) afforded **7** (2.30 g, 85%); white needles, mp 92–94 °C; IR (KBr) ν_{max}: 2929, 1735, 1671, 1523, 1404, 1344, 1267, 1069, 990, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42 (1H, d, J = 5.3 Hz, H-2), 7.10 (1H, d, J = 5.3 Hz, H-3), 3.77 (3H, s, COO*CH*$_3$), 3.58 (1H, dd, J = 8.9, 4.8 Hz, H-5), 3.04–3.17 (2H, m, H-7), 2.43–2.63 (2H, m, H-6); FAB-MS (pos.): *m*/*z* 211 $[M+H]^+$, 421 $[2M+H]^+$.

4.6. 5-Acetyl-4-hydroxy-1-methyl-indole (8)

A mixture of **4** (1.20 g, 6.2 mmol) and DDQ (1.60 g, 7.44 mmol) in dry dioxane (20 mL) were heated under reflux for 4 h. The resulting mixture was cooled in an ice bath and solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure and purified by flash chromatography over silica gel, eluted with hexane–ethyl acetate (9:1) afforded **8** (0.76 g, 64%); white crystals, mp 82–83 °C; IR (KBr) ν_{max}: 3430, 2980, 1630, 1601, 1356, 1322, 1264, 1163, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.65 (1H, s, chelated hydroxyl), 7.48 (1H, d, J = 8.8 Hz, H-6), 6.95 (1H, d, J = 3.0 Hz, H-2), 6.75–6.81 (2H, m, H-3, H-7), 3.76 (3H, s, NCH_3), 2.62 (3H, s, CO*CH*$_3$); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 203.9 (*CO*CH_3), 159.9 (C-4), 141.7 (C-8), 128.6 (C-2), 124.4 (C-6), 118.3 (C-9), 111.5 (C-5), 101.9 (C-3), 101.7 (C-7), 33.4 (NCH_3), 27.0 (CO*CH*$_3$); FAB-MS (+ve): 189 $[M]^+$, 190 $[M+H]^+$, 379 $[2M+H]^+$.

4.7. 1-(4-Hydroxy-benzo[*b*]thiophen-5-yl)-ethanone (9)

The procedure for the synthesis of **8** was repeated (see Section 4.6) with **5** (1.50 g, 7.7 mmol) and DDQ (2.10 g, 9.20 mmol) gave **9** (1.26 g, 85%); white crystals, mp 102–103 °C; IR (KBr) ν_{max}: 3455, 3092, 1629, 1544, 1443, 1410, 1368, 1267, 1164, 988, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.4 (1H, s, OH-chelated), 7.63 (1H, d, J = 5.5 Hz, H-2″), 7.59 (1H, d, J = 8.7 Hz, H-6), 7.36 (1H, d, J = 5.5 Hz, H-3″), 7.33 (1H, d, J = 8.8 Hz, H-5), 2.66 (3H, s, CO*CH*$_3$); FAB-MS (pos.): *m*/*z* 193 $[M+H]^+$, 385 $[2M+H]^+$.

4.8. 4-Hydroxy-1-methyl-indole-5-carboxylic acid methyl ester (10)

Procedure for the synthesis of **8** was repeated (see Section 4.6) with **6** (1.00 g, 4.8 mmol) and DDQ (1.20 g, 5.3 mmol), gave **10** (0.84 g, 85%); white crystals, mp 87–88 °C; IR (KBr) ν_{max}: 3009, 2954, 1658, 1598, 1422, 1342, 1310, 1257, 1143, 974, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.5 (1H, s, chelated hydroxyl), 7.63 (1H, d, J = 8.8 Hz, H-6), 6.94 (1H, d, J = 3.1 Hz, H-2), 6.80 (1H, d, J = 8.8 Hz, H-7), 6.72 (1H, d, J = 3.1 Hz, H-3), 3.93 (3H, s, COO*CH*$_3$), 3.74 (3H, s, NCH_3); FAB-MS (+ve): 206 $[M+H]^+$, 411 $[2M+H]^+$.

4.9. 4-Hydroxy-benzo[*b*]thiophene-5-carboxylic acid methyl ester (11)

The procedure for the synthesis of **8** was repeated (see 4.6) with **7** (2.00 g, 9.5 mmol) and DDQ (3.09 g, 13.70 mmol) gave **11** (1.54 g, 78%); white needles, mp 98–99 °C; IR (KBr) ν_{max}: 3446, 2948, 1661, 1616, 1548, 1436, 1345, 1267, 1142, 1003, 933, 749, 683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.59 (1H, s, OH-chelated), 7.79 (1H, d, J = 9.0 Hz, H-6), 7.66 (1H, d, J = 6.0 Hz, H-2), 7.41 (1H, d, J = 6 Hz, H-3), 7.39(1H, d, J = 9 Hz, H-7), 4.00 (3H, s, OCH_3); FAB-MS (pos.): *m*/*z* 209 $[M+H]^+$, 417 $[2M+H]^+$, 175.

4.10. 1-(4-Methoxy-1-methyl-1*H*-indol-5-yl)-3-phenyl-propenone (12)

To a solution of **8** (200 mg, 1.05 mmol) in ethanol (20 mL) and barium hydroxide (176 mg, 1.05 mmol) was added benzaldehyde (0.42 mL, 4.2 mmol). The reaction mixture was refluxed for 3 h, cooled to room temperature and poured in to water (50 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and combined ethyl acetate extract was washed with satd NH_4Cl solution and brine, dried over Na_2SO_4 and concentrated to afford crude product, which was purified by column chromatography over deactivated silica gel eluted with hexane–ethyl acetate (1:9) afforded **12** (202 mg, 68% yield); yellow crystals, mp 145–146 °C; IR (KBr) ν_{max}: 3411, 2934, 1630, 1583, 1496, 1359, 1306, 1199, 753, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 14.19 (OH-chelated), 7.90 (1H, d, J = 15.5 Hz, H-β), 7.64–7.74 (4H, m, H-α, 6′, 2, 6), 7.40–7.44 (3H, m, H-3, 4, 5), 6.96 (1H, d, J = 3.1 Hz, H-2″), 6.84 (1H, d, J = 8.9 Hz, H-5′), 6.79 (1H, d, J = 3.1 Hz, H-3″), 3.78 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 193.2 (C═O), 161.6 (C-2′), 143.9 (C-β), 141.7 (C-4′), 135.5 (C-1), 130.7 (C-2″), 129.3 (C-3, 5), 128.8 (C-2, 6), 128.6 (C-4), 123.4 (C-α), 121.7 (C-6′), 118.6 (C-1′),

111.7 (C-3′), 102.1 (C-5′), 101.9 (C-3″), 33.5 (NCH_3); FAB-MS (+ve): 278 $[M+H]^+$. Elemental analysis: calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.32; H, 5.03; N, 5.35.

4.11. 1-(4-Methoxy-1-methyl-1*H*-indol-5-yl)-3-(4-methoxy-phenyl)-propenone (13)

Procedure for the synthesis **12** (see Section 4.10) was repeated with **8** (200 mg, 1.05 mmol) and *p*-methoxy-benzaldehyde (0.51 mL, 4.2 mmol), produced **13** (211 mg, 65% yield); yellow crystals, mp 183–184 °C; IR (KBr) ν_{max}: 2925, 2851, 1635, 1603, 1507, 1440, 1359, 1248, 1170, 1126, 1029, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 14.30 (OH-chelated), 7.80 (1H, d, J = 15.3 Hz, H-β), 7.54–7.66 (3H, m, H-6′, 2, 6), 6.93 (2H, d, J = 8.4 Hz, H-3, 5), 6.68–6.83 (3H, m, H-α, 2″, 5′), 6.34 (1H, br s, H-3″), 3.85 (3H, s, OCH_3), 3.63 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 203.3 (C=O), 163.2 (C-2′), 161.6 (C-4), 143.0 (C-4′), 142.4 (C-β), 138.1 (C-1), 130.4 (C-2, 6), 127.7 (C-2″), 124.5 (C-α), 119.6 (C-6′), 116.6 (C-1′), 114.7 (C-3, 5), 111.5 (C-3′), 101.5 (C-3″, 5′), 55.5 (OCH_3), 33.3 (NCH_3); FAB-MS (+ve): 308 $[M+H]^+$ 615 $[2M+H]^+$. Elemental analysis: calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.53; H, 5.37; N, 4.80.

4.12. 1-(4-Hydroxy-benzo[*b*]thiophen-5-yl)-3-phenyl-propenone (14)

The procedure for the synthesis of **12** (see Section 4.10) was repeated with **9** (200 mg, 1.04 mmol) and benzaldehyde (0.52 mL, 5.2 mmol), produced 204 mg (70%) of **14**; yellow needles, mp 144–145 °C; IR (KBr) ν_{max}: 3490, 3090, 1637, 1590, 1499, 1446, 1361, 1205, 1092, 975, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 14.14 (OH-chelated), 7.96 (1H, d, J = 15.4 Hz, H-β), 7.82 (1H, d, J = 8.7 Hz, H-6′), 7.67–7.74 (4H, m, H-α, 2, 6, 2″), 7.42–7.46 (4H, m, H-3, 4, 5, 5′), 7.39 (1H, d, J = 5.3 Hz, H-3″); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 193.9 (C=O), 161.3 (C-2′), 148.1 (C-4′), 145.4 (C-β), 135.1 (C-1), 131.2 (C-4), 131.0 (C-3′), 129.4 (C-3, 5), 129.0 (C-2, 6), 125.8 (C-2″), 124.7 (C-α), 122.3 (C-6′), 120.9 (C-3″), 114.8 (C-1′), 113.3 (C-5′); FAB-MS (+ve): 281 $[M+H]^+$. Elemental analysis: calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.31; S, 11.44. Found: C, 73.04; H, 4.51; S, 11.69.

4.13. 1-(4-Hydroxy-benzo[*b*]thiophen-5-yl)-3-(4-methoxy-phenyl)-propenone (15)

The procedure for the synthesis of **12** (see Section 4.10) was repeated with **9** (200 mg, 1.04 mmol) and *p*-methoxy-benzaldehyde (0.63 mL, 5.2 mmol), produced 210 mg (65%) of **15**; yellow needles, mp 163–164 °C; IR (KBr) ν_{max}: 3424, 2930, 1645, 1602, 1509, 1439, 1357, 1263, 1175, 1089, 1024, 788, 678 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 14.25 (OH-chelated), 7.89 (1H, d, J = 15.3 Hz, H-β), 7.81 (1H, d, J = 8.7 Hz, H-6′), 7.61–7.69 (3H, m, H-2, 6, 2″), 7.57 (1H, d, J = 15.2 Hz, H-α), 7.38 (1H, d, J = 8.9 Hz, H-5′), 7.37 (1H, d, J = 5.3 Hz, H-3″), 6.95 (2H, d, J = 8.6 Hz, H-3, 5), 3.86 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 193.9 (C=O), 162.3 (C-2′), 161.3 (C-4), 147.8 (C-4′), 145.3 (C-β), 130.9 (C-1), 130.9 (C-2, 6), 127.9 (C-3′), 125.7 (C-2″), 124.7 (C-α), 122.3 (C-6′), 118.4 (C-3″), 114.9 (C-1′), 114.9 (C-3, 5′), 113.2(C-5′), 55.8 (OCH_3); FAB-MS (+ve): 311 $[M+H]^+$, 621 $[2M+H]^+$. Elemental analysis: calcd for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55; S, 10.33. Found: C, 69.53; H, 4.72; S, 10.55.

4.14. 4-Methoxy-1-methyl-indole-5-carboxylic acid methyl ester (16)

To a stirred mixture of phenol **10** (0.50 g, 1.2 mmol) and potassium bicarbonate (0.60 g, 6 mmol) in acetone (20 mL) was added methyl iodide (1.70 g, 12 mmol) and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled, filtered through Celite. The filtrate was concentrated and purified by column chromatography over silica gel, eluted with hexane–ethyl acetate (9:1) afforded quantitative yield of **16** (0.50 g) as a sticky mass; IR (KBr) ν_{max}: 3014, 2948, 1712, 1605, 1572, 1488, 1310, 1257, 1195, 1051, 951, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.74 (1H, d, J = 8.6 Hz, H-6), 7.05 (1H, d, J = 8.6 Hz, H-7), 7.02 (1H, d, J = 3.0 Hz, H-2), 6.69 (1H, d, J = 3.0 Hz, H-3), 4.10 (3H, s, OCH_3), 3.91 (3H, s, OMe-11), 3.76 (3H, s, NCH_3); FAB-MS (+ve): 219 $[M]^+$, 220 $[M+H]^+$.

4.15. 4-Methoxy-benzo[*b*]thiophene-5-carboxylic acid methyl ester (17)

The procedure for the synthesis of **16** (see Section 4.14) was repeated with **11** (0.50 g, 2.4 mmol), methyl iodide (0.15 mL, 24 mmol) and potassium carbonate (1.65 g, 12 mmol), afforded **17** (0.47 g, 90%); white needles, mp 50–51 °C; IR (KBr) ν_{max}: 3021, 2930, 1719, 1591, 1454, 1335, 1193, 1018, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.80 (1H, d, J = 8.5 Hz, H-6), 7.63 (1H, d, J = 8.4 Hz, H-7), 7.54 (1H, d, J = 5.5 Hz, H-2), 7.44 (1H, d, J = 5.5 Hz, H-3), 4.04 (3H, s, OCH_3), 3.95 (3H, s, $COOCH_3$); FAB-MS (pos.): *m*/*z* 222, 223 $[M+H]^+$, 445 $[2M+H]^+$.

4.16. 3-Hydroxy-1-(4-methoxy-1-methyl-1*H*-indol-5-yl)-3-phenyl-propenone (18)

To a stirred solution of acetophenone (1.36 g, 0.011 mol) and sodium amide (0.53 g, 0.013 mol) in ether (80 mL) was added **16** (0.50 g, 0.002 mol) in ether (15 mL) at room temperature. The reaction mixture was refluxed for 4 h. Cooled reaction mixture was quenched by drop wise addition of aqueous ammonium chloride solution (10 mL), poured over ice cold saturated solution NH_4Cl (50 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure. The resulting residue was purified by column chromatography over silica gel eluting with 5% ethyl acetate in hexane to give **18** (300 mg, 40%); viscous, IR (KBr) ν_{max}: 3439, 2934, 1660, 1601, 1499, 1450, 1272, 1218, 760, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 17.0 (1H, s, chelated hydroxyl), 8.00 (2H, br dd, H-2′, 6′), 7.86 (1H, d, J = 8.7 Hz, H-6), 7.52

(3H, m, H-3′, 4′, 5′), 7.34 (1H, s, H-8), 7.13 (1H, d, $J = 8.7$ Hz, H-5), 7.06 (1H, d, $J = 2.9$ Hz, H-2′), 6.72 (1H, d, $J = 2.86$ Hz, H-3″), 4.02 (3H, s, OCH_3), 3.81 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 186.9 (C-7), 183.5 (C-9), 154.4 (C-2), 140.9 (C-4), 133.0 (C-1′), 131.7 (C-2′), 128.9 (C-4′), 128.3 (C-2′, 6′), 126.9 (C-3′, 5′), 123.5 (C-6), 121.1 (C-1), 118.6 (C-3), 105.2 (C-3″), 100.4 (C-5), 97.6 (C-8), 33.5 (NCH_3); FAB-MS (+ve): 308 $[M+H]^+$. Elemental analysis: calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.72; H, 5.63; N, 4.66.

4.17. 3-Hydroxy-1-(4-methoxy-benzo[*b*]thiophen-5-yl)-3-phenyl-propenone-4-oxo-4-thiophen-2-yl-butyric acid (19)

The procedure for the synthesis of **18** (see Section 4.16) was repeated with **17** (200 mg, 0.90 mmol) and enolate of acetophenone (0.52 mL, 4.5 mmol), produced 82.5 mg (35% yield) of **19**; viscous; IR (KBr) ν_{max}: 3432, 3019, 1594, 1459, 1416, 1331, 1217, 1013, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 16.87 (1H, s, OH-chelated), 8.02 (3H, br d, $J = 7.2$ Hz, H-2′, 6′, H-2), 7.90 (1H, d, $J = 8.4$ Hz, H-6), 7.74 (1H, d, $J = 8.4$ Hz, H-7), 7.57 (3H, m, H-3′, 4′, 5′), 7.50 (1H, s, H-11), 7.49 (1H, d, $J = 5.7$ Hz, H-3), 4.03 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 186.1 (C-10), 185.1 (C-12), 155.6 (C-4), 145.4 (C-8), 135.9 (C-1′), 134.9 (C-9), 132.7 (C-4′), 129.0 (C-3′, 5′), 127.6 (C-2′, 6′), 127.3 (C-2), 125.9 (C-6), 124.7 (C-5), 121.5 (C-3), 118.9 (C-7), 98.1 (C-11), 63.1 (OCH_3); FAB-MS (pos.): *m*/*z* 311 $[M+H]^+$, 621 $[2M+H]^+$. Elemental analysis: calcd for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55; S, 10.33. Found: C, 69.39; H, 4.73; S, 10.17.

4.18. 1-(4-Hydroxy-1-methyl-1*H*-indol-5-yl)-2-methanesulfinyl-ethanone (20)

A mixture of dry DMSO (1.5 mL) and sodium hydride (280 mg, 11.6 mmol) in dry benzene (20 mL) was heated at 80 °C under nitrogen atmosphere for 2 h. The solution was cooled to room temperature and added drop wise **10** (200 mg, 0.97 mmol) in dry benzene (5 mL). The reaction mixture was then stirred for 1 h, diluted with ether (40 mL) and quenched with saturated solution of NH_4Cl (20 mL). Organic and aqueous layers were separated and the aqueous layer was further extracted with ether (3×30 mL). Combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate, afforded **20** (195 mg, 80%); white crystals, mp 138–139 °C; IR (KBr) ν_{max}: 3422, 2951, 1628, 1602, 1499, 1435, 1349, 1271, 1198, 1016, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.46 (1H, d, $J = 8.9$ Hz, H-6), 6.98 (1H, d, $J = 3.1$ Hz, H-2), 6.86 (1H, d, $J = 8.9$ Hz, H-7), 6.77 (1H, d, $J = 3.0$ Hz, H-3), 4.52 (1H, d, $J = 13.8$ Hz, H-11a), 4.26 (1H, d, $J = 13.8$ Hz, H-11b) 3.78 (3H, s, NCH_3), 2.77 (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 195.4 (C-10), 160.9 (C-4), 142.2 (C-8), 129.1 (C-2), 124.2 (C-6), 118.2 (C-9), 111.4 (C-5), 103.1 (C-3), 102.2 (C-7), 62.6 (C-11), 39.9 ($SOCH_3$), 33.6 (NCH_3); FAB-MS (+ve): 252 $[M+H]^+$, 503 $[2M+H]^+$.

4.19. 1-(4-Hydroxy-benzo[*b*]thiophen-5-yl)-2-methanesulfinyl-ethanone (21)

The procedure for the synthesis of **20** (see Section 4.18) was repeated with **11** (250 mg, 1.12 mmol) and enolate of DMSO in DMSO (1.5 mL), produced 228 mg (80%) of **21**; white crystals, mp 120–121 °C; IR (KBr) ν_{max}: 3455, 3092, 1629, 1544, 1443, 1410, 1368, 1267, 1164, 988, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 13.4 (1H, s, OH-chelated), 7.75 (1H, d, $J = 8.7$ Hz, H-6), 7.64 (1H, d, $J = 5.5$ Hz, H-2″), 7.50 (1H, d, $J = 5.5$ Hz, H-3″), 7.44 (1H, d, $J = 8.7$ Hz, H-5), 4.63 (1H, d, $J = 14.2$ Hz, H-8_a), 4.52 (1H, d, $J = 14.2$ Hz, H-8_b), 2.80 (3H, s, $SOCH_3$); FAB-MS (pos.): *m*/*z* 255 $[M+H]^+$, 509 $[2M+H]^+$.

4.20. 7-Methyl-2-phenyl-7*H*-pyrano[2,3-*e*]indol-4-one (22)

Benzaldehyde (1.4 mL, 14 mmol) in dry toluene was slowly added to a warm solution of **20** (350 mg, 1.4 mmol) in dry toluene (15 mL) containing catalytic amount of piperidine (four drops) and the resulting mixture was allowed to reflux for 3 h. After distillation of solvent, residue was purified by column chromatography over silica gel (eluting with 15% ethyl acetate and hexane) to afford **22** (268 mg, 70%); yellow crystals, mp 178–179 °C; IR (KBr) ν_{max}: 2950, 1631, 1594, 1499, 1414, 1355, 1251, 1133, 1051, 769, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.95–8.03 (3H, m, H-2′, 6′, 5), 7.51–7.54 (3H, m, H-3′, 4′, 5′), 7.33 (1H, d, $J = 8.7$ Hz, H-6), 7.14 (1H, d, $J = 3.0$ Hz, H-2′), 6.92 (1H, d, $J = 3.0$ Hz, H-3″), 6.86 (1H, s, H-3), 3.86 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 179.2 (C-4), 162.3 (C-2), 151.5 (C-9), 140.2 (C-7), 132.6 (C-1′), 131.5 (C-2′), 129.6 (C-4′), 129.4 (C-3′, 5′), 126.5 (C-2′, 6′), 118.7 (C-5), 117.6 (C-10), 116.9 (C-8), 108.5 (C-3′), 108.2 (C-6), 100.1 (C-3), 33.7 (NCH_3); FAB-MS (+ve): 276 $[M+H]^+$. Elemental analysis: calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.74; H, 4.43; N, 5.37.

4.21. 2-(4-Methoxy-phenyl)-7-methyl-7*H*-pyrano[2,3-*e*]-indol-4-one (23)

The procedure for the synthesis of **22** (see Section 4.18) was repeated with *p*-methoxy-benzaldehyde (1.4 mL, 12.3 mmol) and **20** (310 mg, 1.23 mmol), afforded **23** (280 mg, 74%); yellow crystals, mp 208–209 °C; IR (KBr) ν_{max}: 2951, 1625, 1597, 1352, 1175, 1055, 767, 586 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.97 (1H, d, $J = 8.7$ Hz, H-5), 7.88 (2H, br d, $J = 8.9$, 2.0 Hz, H-2′, 6′), 7.27 (1H, br d, $J = 8.7$, 1.7 Hz, H-6), 7.10 (1H, d, $J = 3.7$ Hz, H-2′), 7.00 (2H, br d, $J = 8.9$, 1.9 Hz H-3′, 5′), 6.88 (1H, br d, $J = 3.02$, 0.34 Hz, H-3″), 6.73 (1H, s, H-3), 3.86 (3H, s, OCH_3), 3.82 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 179.1 (C-4), 162.4 (C-2), 162.3 (C-4′), 151.6 (C-9), 140.1 (C-7), 129.5 (C-2′), 128.0 (C-2′, 6′), 124.9 (C-1′), 118.6 (C-5), 117.5 (C-10), 116.7 (C-8), 114.7 (C-3′, 5′), 108.3 (C-6), 106.7 (C-3″), 100.0 (C-3), 55.8 (OCH_3), 33.6 (NCH_3); FAB-MS (+ve): 306 $[M+H]^+$. Elemental analysis: calcd for

$C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.92; H, 5.13; N, 4.75.

4.22. 8-Phenyl-9-oxa-3-thia-cyclopenta[*a*]naphthalen-6-one (24)

The procedure for the synthesis of **22** (see Section 4.18) was repeated with benzaldehyde (0.80 mL, 7.80 mmol) with **21** (200 mg, 0.78 mmol) afforded **24** (166 mg, 76%); white crystals, mp 194–195 °C; IR (KBr) ν_{max}: 3060, 2928, 1653, 1596, 1491, 1447, 1385, 1353, 1093, 808, 767, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.10 (1H, d, J = 8.6 Hz, H-5), 7.95 (2H, m, H-2′, 6′), 7.82 (1H, d, J = 5.4 Hz, H-2′), 7.80 (1H, dd, J = 8.7, 0.5 Hz, H-6), 7.58 (1H, d, J = 5.4 Hz, H-3″), 7.54 (3H, m, H-3′, 4′, 5′), 6.87 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 178.5 (C-4), 162.7 (C-2), 152.3 (C-9), 146.8 (C-7), 132.2 (C-8), 132.1 (C-1′), 131.9 (C-4′), 129.6 (C-2′), 129.5 (C-3′, 5′), 128.2 (2″), 126.5 (C-2′, 6′), 121.1 (C-5), 120.6 (C-3″), 120.4 (C-10), 119.9 (C-6), 108.6 (C-3); FAB-MS (+ve): 279 $[M+H]^+$. Elemental analysis: calcd for $C_{17}H_{10}O_2S$: C, 73.36; H, 3.62; S, 11.52. Found: C, 73.54; H, 3.86; S, 11.39.

4.23. 3-Hydroxy-7-methyl-2-phenyl-7*H*-pyrano[2,3-*e*]-indol-4-one (25)

To a stirred solution of chalcone **12** (200 mg, 0.72 mmol) in ethanol (10 mL) at 0 °C, was added 10% aqueous potassium hydroxide (3.6 mL) and 8% hydrogen peroxide (0.40 mL). The reaction mixture was stirred at 0 °C for 5 h. The reaction mixture was diluted with water (25 mL), extracted with ethyl acetate (3 × 50 mL) and the extract was washed with water, saturated NH_4Cl and finally with brine. The organic layer separated, dried over Na_2SO_3, concentrated and purified by chromatographic separation over deactivated silica gel using benzene as eluent to afford flavonols, **25** (124 mg, 59%) along with two minor products flavanone, **28** (6 mg, 3%) and flavanonol, **29** (10.5 mg, 5%).

4.23.1. Compound 25. Yellow crystals, mp 196–197 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.32 (2H, d, J = 7.8 Hz, H-2′, 6′), 8.00 (1H, d, J = 8.7 Hz, H-5), 7.56 (2H, t, J = 7.8 Hz, H-3′, 5′), 7.46 (1H, br t, J = 7.5 Hz, H-4′), 7.36 (1H, d, J = 8.7 Hz, H-6), 7.15 (1H, d, J = 3.0 Hz, H-2′), 6.98 (1H, d, J = 2.4 Hz, H-3″), 3.89 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 194.0 (C-4), 151.6 (C-2), 143.3 (C-9), 142.4 (C-7), 138.7 (C-3), 132.0 (C-1′), 129.9 (C-2′), 129.4 (C-4′), 128.9 (C-3′, 5′), 127.8 (C-2′, 6′), 118.5 (C-5), 118.2 (C-10), 113.7 (C-8), 108.6 (C-6), 100.4 (C-3″), 33.7 (NCH_3); FAB-MS (pos.): m/z 292 $[M+H]^+$. Elemental analysis: calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.46; H, 4.25; N, 4.99.

4.23.2. Compound 28. Yellow crystals, mp 149–150 °C, t_R 12.88 min, RP-HPLC on ODS column (Whatman, 5 μm, 6.35 × 250 mm, λ 254 nm) using isocratic system comprised of MeOH–H_2O–AcOH (85:15:1) in 20 min at flow rate of 0.5 mL/min; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.79 (1H, d, J = 8.7 Hz, H-5), 7.55 (2H, m, H-2′, 6′), 7.38–7.49 (3H, m, H-3′, 4′, 5′), 6.96–7.01 (2H, m, H-6, 2′), 6.69 (1H, d, J = 3.1 Hz, H-3″), 5.62 (1H, dd, J_{aa} = 12.8 Hz, J_{ee} = 3.3 Hz, H-2ax), 3.79 (3H, s, NCH_3), 3.13 (1H, dd, J_{gem} = 16.7 Hz J_{aa} = 12.9 Hz, H-3ax), 2.91 (1H, dd, J_{gem} = 16.7 Hz J_{ea} = 3.3 Hz, H-3eq); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 191.7 (C-4), 152.4 (C-9), 141.9 (C-7), 139.7 (C-1′), 129.0 (C-3′, 5′), 128.9 (C-2′), 128.8 (C-4′), 126.4 (C-2′, 6′), 120.7 (C-5), 118.2 (C-10), 112.9 (C-8), 104.5 (C-6), 101.1 (C-3″), 80.3 (C-2), 44.7 (C-3), 33.5 (NCH_3); FAB-MS (pos.): m/z 278 $[M+H]^+$.

4.23.3. Compound 29. White crystals, mp 208–209 °C, t_R 12.36 min, RP-HPLC on ODS column (Whatman, 5 μm, 6.35 × 250 mm, λ 254 nm) using isocratic system comprised of MeOH–H_2O–AcOH (85:15:1) in 20 min at flow rate of 0.5 mL/min; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75 (1H, d, J = 8.7 Hz, H-5), 7.64–7.68 (2H, m, H-2′, 6′), 7.44–7.53 (3H, m, H-3′, 4′, 5′), 7.03 (1H, d, J = 8.8 Hz, H-6), 7.00 (1H, d, J = 3.2 Hz, H-2′), 6.66 (1H, d, J = 3.1 Hz, H-3′), 5.28 (1H, d, J_{aa} = 12.2 Hz, H-2ax), 4.64 (1H, d, J_{aa} = 12.2 Hz, H-3ax), 3.81 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 193.7 (C-4), 161.6 (C-9), 142.3 (C-7), 137.4 (C-1′), 129.4 (C-2′, 4′), 128.9 (C-3′, 5′), 128.0 (C-2′, 6′), 120.7 (C-5), 118.5 (C-10), 110.0 (C-8), 105.2 (C-6), 101.3 (C-3″), 84.7 (C-2), 73.5 (C-3), 33.6 (NCH_3); FAB-MS (pos.): m/z 294 $[M+H]^+$.

4.23.4. 7-Hydroxy-8-phenyl-9-oxa-3-thia-cyclopenta[*a*]-naphthalen-6-one (26). The procedure for the synthesis of **25** (see Section 4.23) was repeated with chalcone **14** (200 mg, 0.71 mmol) and hydrogen peroxide (0.40 mL), afforded **26** (143 mg, 68%); brown needles, mp 224–226 °C; IR (KBr) ν_{max}: 3284, 2924, 1639, 1605, 1589, 1491, 1377, 1218, 1122, 1033, 748, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.29 (2H, br d, J = 7.7 Hz, H-2′, 6′), 8.11 (1H, d, J = 8.6 Hz, H-5), 7.88 (1H, d, J = 5.3 Hz, H-2″), 7.81 (1H, d, J = 8.6 Hz, H-6), 7.61 (1H, d, J = 5.4 Hz, H-3″), 7.47–7.56 (3H, m, H-3′, 4′, 5′); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 173.6 (C-4), 151.7 (C-2), 145.6 (C-9), 144.1 (C-7), 139.3 (C-3), 131.6 (C-1′), 130.4 (C-4′), 129.6 (C-8), 129.1 (C-3′, 5′), 128.2 (C-2′), 127.9 (C-2′, 6″), 120.8 (C-3′), 120.8 (C-5), 119.6 (C-6), 117.0 (C-10); FAB-MS (pos.): m/z 295 $[M+H]^+$, 589 $[2M+H]^+$. Elemental analysis: calcd for $C_{17}H_{10}O_3S$: C, 67.37; H, 3.42; S, 10.89. Found: C, 67.55; H, 3.46; S, 11.03.

4.24. 7-Hydroxy-8-(4-methoxy-phenyl)-9-oxa-3-thia-cyclopenta[*a*]naphthalen-6-one (27)

The procedure for the synthesis of **25** (see Section 4.23) was repeated with chalcone **15** (200 mg, 0.64 mmol) and hydrogen peroxide (0.40 mL), afforded **27** (135 mg, 65%); dirty yellow amorphous powder; IR (KBr) ν_{max}: 3448, 2925, 1630, 1598, 1459, 1418, 1350, 1259, 1179, 1114, 1028, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 8.85 (1H, br s, OH), 8.31 (2H, d, J = 8.5 Hz, H-2′, 6′), 8.08 (1H, *d*, J = 8.6 Hz, H-5), 7.94 (1H, d, J = 4.8 Hz, H-2′), 7.88 (1H, br d, H-6), 7.77 (1H, d, J = 4.6 Hz, H-3″), 7.07 (2H, d, J = 8.7 Hz, H-3′, 6′), 3.90 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.0 (C-4), 161.0 (C-4′), 151.1

(C-9), 145.0 (C-2), 144.3 (C-7), 138.1 (C-3), 132.3 (C-1′), 129.3 (C-2′, 6′), 127.7 (C-2′), 123.7 (C-8), 120.4 (C-3′, 5′ and C-5), 119.1 (C-3″), 116.7 (C-10), 114.2 (C-6), 55.4 (OCH_3); FAB-MS (pos.): *m/z* 325 $[M+H]^+$, 649 $[2M+H]^+$. Elemental analysis: calcd for $C_{18}H_{12}O_4S$: C, 66.65; H, 3.73; S, 9.89. Found: C, 66.94; H, 3.58; S, 9.97.

4.25. Biological evaluation

The fungal and the bacterial strains were grown on Sabroaud dextrose agar and nutrient agar media respectively. After the incubation fungal and bacterial growth were suspended in normal saline and maintained at $1.0–5.0 \times 10^3$ cfu/mL. The activity of compounds was determined by the NCCLS method for fungus using RPMI-1640 media buffered with MOPS (3-[*N*-morpholino]propanesulfonic acid) (Sigma Chemical Co.) and Mueller Hinton broth for bacteria. The 96-well tissue culture plates were used for twofold serial dilution. The proper growth control, drug control and the blank were adjusted onto the plate. Compounds were dissolved in DMSO at a concentration of 1 mg/mL and 20 μL of this was added to 96-well tissue culture plate having 180 μL RPMI-1640 so the maximum concentration of the compound became 50 μg/mL. From here the solution was serially diluted resulting into the half of the concentration of test compounds and then inoculum was added and kept for incubation. Micro-titer plates were incubated at 35 °C in a moist, dark chamber and MICs were recorded spectrophotometrically.

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