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Design and synthesis of new series of coumarin–aminopyran derivatives possessing potential anti-depressant-like activity ☆

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ABSTRACT

A new series of coumarin based aminopyran derivatives were designed, synthesized and evaluated for their preclinical antidepressant effect on Swiss albino mice. Among the series, compounds **21**, **25**, **26**, **27**, **32** and **33** exhibited significant activity profile in forced swimming test (FST). Compound **27** was most efficacious, which at a very low dose of 0.5 mg/kg reduced the time of immobility by 86.5% as compared to the standard drug fluoxetine (FXT) which reduced the immobility time by 69.8% at the dose of 20 mg/kg, ip. In addition, all active compounds were screened in dose dependent manner (at doses of 0.25, 0.5, 1 mg/kg ip) in FST and tail suspension test (TST). Interestingly, all active compounds did not caused any significant alteration of locomotor activity in mice as compared to control, indicating that the hybrids did not produce any motor impairment effects. The results indicate that coumarin–aminopyran derivatives may have potential therapeutic value for the management of mental depression.

Major depression disorder (MDD) is described as a depressive state of mind, which is associated with faulty mood, loss of interest, disruption in sleep patterns, fatigue and sometimes suicidal tendencies. It is a chronic and life-threatening mental illness, which remains hidden and untreated at most of the times.[1] World Health Organisation (WHO) had estimated that 'at least 350 million people live with depression and it is the leading cause of disability worldwide'.[2] Epidemiological studies have indicated that about 2/3 of people who commit suicide are depressed at the time of their death.[3] Exact cause of depression is not clearly known, but it is believed that imbalance of neurotransmitters in brain, genetic vulnerability, stressful life events and medical problems are the main factors leading to depression.[4] Currently available antidepressant treatments are selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRI) and some nonmedication therapeutic options.[5]

Even though wide range of conventional therapies is available, nearly 15% of depressed people are still refractory to the current existing therapies.[6] In addition, most of the people suffer from relapse and experience serious side effects after treatment with current therapies.[7] In Feb 2007, the USFDA displayed 'black box' label on currently available antidepressants indicating that their use may increase the risk of suicidal thinking behaviour in few cases of children, adolescents and adults.[8] Hence, there is an urgent need to develop new class of prototypes that are more effective, tolerable and safe in depressed individuals against this deadly disorder.

Coumarins are prominent class of benzopyrones, which belong to natural as well as synthetic origin that exhibit diverse biological activities.[9] Many reports suggest that coumarins and their synthetic analogues possess antidepressant properties.[10] Coumarin containing natural product scopoletin, isolated from the *Polygala sabulosa* was found to have significant in vivo antidepressant activity.[11] In addition, xanthotoxin and praeruptorin-A belongs to the new generation of MAOIs exhibiting potent antidepressant properties.[12] Our research group has been involved for past several years in the development of 3-phenylcoumarin based scaffolds as potential antidepressant agents, which significantly decreased the immobility time compared to the standard drug fluoxetine (FXT), (Fig. 1).[13] The promising hit compound may serve as a valuable template to design further analogue to improve activity and efficacy.[14]

During recent years aminopyran containing compounds have shown prominent antidepressant activity.[15] Dutta et al. have

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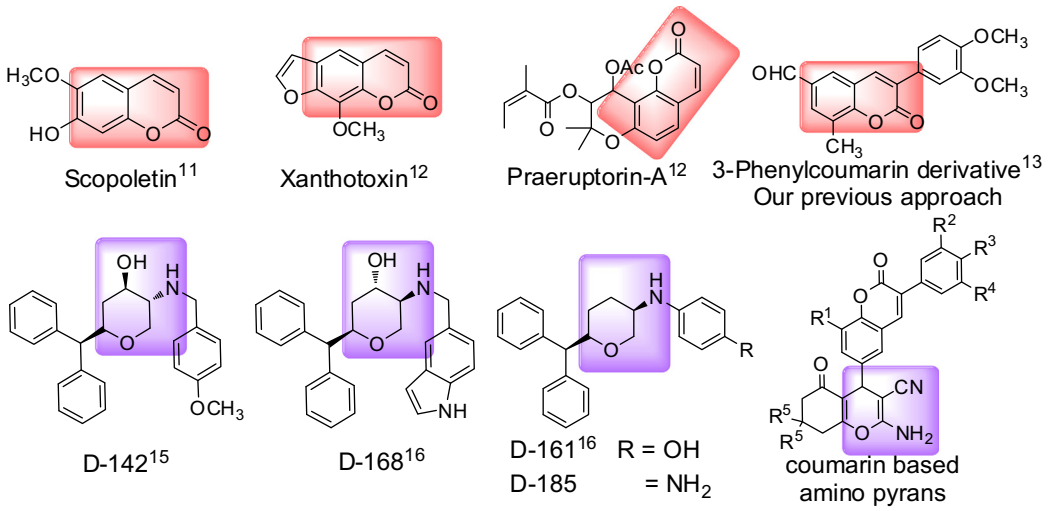
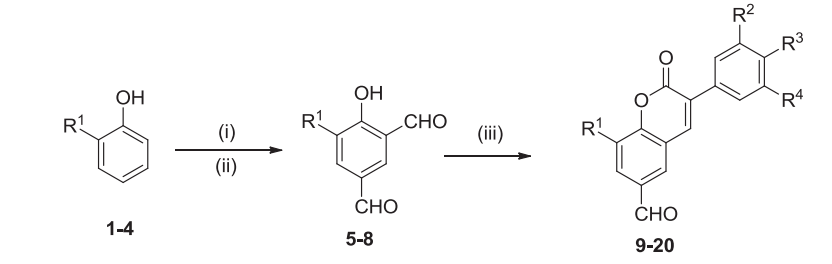


Figure 1. Designing of coumarin–aminopyran hybrids based on coumarin and aminopyran scaffolds showing antidepressant activity.



	R^1
1,5	CH_3
2,6	Isopropyl
3,7	*Sec*-butyl
4,8	*Tert*-butyl

	R^1	R^2	R^3	R^4
9	CH_3	H	OCH_3	H
10	CH_3	H	OCH_3	OCH_3
11	CH_3	OCH_3	OCH_3	OCH_3
12	Isopropyl	H	OCH_3	H
13	Isopropyl	H	OCH_3	OCH_3
14	Isopropyl	OCH_3	OCH_3	OCH_3
15	*Sec*-butyl	H	OCH_3	H
16	*Sec*-butyl	H	OCH_3	OCH_3
17	*Sec*-butyl	OCH_3	OCH_3	OCH_3
18	*Tert*-butyl	H	OCH_3	H
19	*Tert*-butyl	H	OCH_3	OCH_3
20	*Tert*-butyl	OCH_3	OCH_3	OCH_3

	R^1	R^2	R^3	R^4	R^5
21	Isopropyl	H	OCH_3	H	CH_3
22	CH_3	H	OCH_3	OCH_3	CH_3
23	CH_3	OCH_3	OCH_3	OCH_3	H
24	CH_3	OCH_3	OCH_3	OCH_3	CH_3
25	Isopropyl	H	OCH_3	H	H
26	Isopropyl	H	OCH_3	OCH_3	H
27	Isopropyl	H	OCH_3	OCH_3	CH_3
28	Isopropyl	OCH_3	OCH_3	OCH_3	H
29	Isopropyl	OCH_3	OCH_3	OCH_3	CH_3
30	*Sec*-butyl	H	OCH_3	H	H

	R^1	R^2	R^3	R^4	R^5
31	*Sec*-butyl	H	OCH_3	H	CH_3
32	*Sec*-butyl	H	OCH_3	OCH_3	CH_3
33	*Sec*-butyl	OCH_3	OCH_3	OCH_3	H
34	*Sec*-butyl	OCH_3	OCH_3	OCH_3	CH_3
35	*Tert*-butyl	H	OCH_3	H	H
36	*Tert*-butyl	H	OCH_3	H	CH_3
37	*Tert*-butyl	H	OCH_3	OCH_3	H
38	*Tert*-butyl	H	OCH_3	OCH_3	CH_3
39	*Tert*-butyl	OCH_3	OCH_3	OCH_3	H
40	*Tert*-butyl	OCH_3	OCH_3	OCH_3	CH_3

Scheme 1. Synthesis of 3-aryl coumarin based aminopyran derivatives. Reagents and conditions: (i) HMTA, TFA, 120 °C, 4 h. (ii) aq H_2SO_4, 100 °C, 2 h. (iii) appropriate phenylaceticacid, cyanuric chloride, NMM, DMF, 110 °C, 30–90 min, (vi) malononitrile, different 1,3-cyclohexadiones, DMAP, EtOH, reflux, 0.5 h.

synthesized a series of substituted aminopyran derivatives, as new generation of triple reuptake inhibitors (TRI) and observed significant antidepressant effects.[16] In the search of drug like molecules, molecular hybridisation technique is an emerging strategy in which two active pharmacophores are fused in a single frame work.[17] The resultant hybrid molecule may modulate the potency and efficacy, compared to that of parent subunits. Thus inspired from the molecular hybridisation approach,[18–20] we have rationally designed and synthesized some new 3-phenylcoumarin-aminopyran hybrids for a possible antidepressant activity.

The synthesis of intermediate and final compounds is described in the scheme 1. The Duff reaction on *ortho*-substituted phenols