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Analgesic and antiinflammatory evaluation of newer 2-amino nicotinate derivatives synthesized by baylis hillman reaction

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Abstract

Nicotine is an important class of heterocyclic compound, has been shown to exhibit diverse biological and pharmacological activities. In this study, a series of newer 2-amino nicotinate derivativeshave been synthesized by Baylis Hillman reaction. All the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the synthesized compounds were tested for their analgesic and anti-inflammatory activities. The compounds exhibited significant analgesic and anti-inflammatory activities. These compounds can be further exploited to get the potent lead compounds. The detailed synthesis and the pharmacological screening of 2-amino nicotinate derivatives are reported.

Keywords: Nicotinic acid, Baylis Hillman reaction, FT-IR, Analgesic, Anti-inflammatory.

1. Introduction

In synthetic organic chemistry the most continuing sophistication atom reaction is Baylis Hillman reaction that results in the formation of carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles with suitable catalyst DABCO(1,2-diazabicyclo [2,2,2]octane producing Baylis Hillman Adducts which contain hydroxyl group, double bond, electron withdrawing group which readily transforms into the acetates. Furthermore it is a three-step reaction involving successive Michael, aldol, and elimination reactions in one-pot. Thus resulting MBH adducts found many applications in the synthesis of medicinally relevant compounds as well as some complex natural products.

The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years mainly because of their important biological properties. Nicotine are six membered heterocyclic compound, have some structural feature with one nitrogen atom. Nicotine and its derivatives, a class of well-known nitrogen heterocycles, occupy a prime position in medicinal chemistry for their diverse biological activities. They have been known to exhibit antimicrobial [1, 2], analgesic [3, 4], anticancer [5, 6], anti-tubercular [7, 8], anti-inflammatory [9, 10], anticonvulsant [11, 12], hypoglycemic [13], antipyretic [14], antihelmintic [15], antioxidant [16] and herbicidal properties.

Considering the above observations and in connection to previous publications involving the synthesis of new biologically active heterocycles. Substitution of the heterocyclic moieties on the nicotine ring is anticipated to have potential biological activity. In the present communication synthesis, characterization and the biological activity of various nicotine moieties are reported. Thus the efficient synthesis newer 2-amino nicotinate derivatives still represent highly pursued target.

2. Experimental

2.1 Material and Methods

All the chemicals used were of laboratory grade and procured from E. Merck, Germany; Qualigens, Mumbai; Sigma Aldrich, USA and S.D. Fine Chemicals, Mumbai. Melting points were determined in digital melting point apparatus and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. All compounds were purified by recrystallization with suitable organic solvents. All the microwave experiments were performed using RAGA's microwave synthesizer. IR spectra were recorded on BROOKER-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a BRUKER Ac 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Purity of the synthesized compounds was checked by HPLC AGILENT. Elemental analysis of the all the synthesized compounds was carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use.

2.2 General experimental Procedure for the Synthesis of Newer2-Aminonicotinate derivatives from Acetylated Baylis-Hillmann adducts and Enamines

To a well-stirred solution of NaH (60% in paraffin oil; 240 mg, 6mmol) in anhydrous THF (15 ml) was added the enamino ester, methyl 3-methylbut-2-enoate (2 mmol) dissolved in anhydrous THF (5 ml) at room temperature under N_2 atmosphere, and the mixture was stirred for 15 min at the same temperature. Then, an acetylated Baylis–Hillman nitrile (2.2 mmol) dissolved in anhydrous THF (5 ml) was added slowly and the mixture was stirred at room temperature until the reaction was completed. After completion, the solvent was removed under reduced pressure and the residue was diluted with ice-cold H_2O (15 ml) and extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with H_2O (10 ml), dried (Na_2SO_4), concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc–hexane, 1:9 followed by 1:4) to afford pure compound.

2.2.1 Methyl 6-amino-5-[(2-trifluromethyl) benzyl)]-2-methyl nicotinate (AN-1): Melting point: 299°C, Yield (%): 55%, TLC [hexane: ethyl acetate (1:1)]: 0.64, IR (KBr): 3439, 3332, 3149, 2953, 2231, 1704, 1658, 1562, 1256, 961 cm^{-1}; ^{1}HNMR($CDCl_3$,300MHz): δ7.48(s,1H), 7.71(d,1H), 7.43(t,1H), 7.36(t,1H), 7.08(d,1H), 4.68(brs.2H), 4.01(S,2H), 3.83(s,3H), 2.70(s,3H); ESI-MS: 325*m/z*.

2.2.2 Methyl 6-amino-5-(2,5-dimethoxybenzyl)-2-methyl nicotinate (AN-2): Melting point: 360°C; Yield: 68%; TLC [Hexane: ethyl acetate (1:1)]: 0.78; IR (KBr): 3424, 3335, 3148, 2967, 2835, 1703, 1667, 1557, 1267, 1075cm^{-1}; ^{1}HNMR($CDCl_3$, 300MHz): δ7.48(s,1H), 7.71(d,1H), 7.43(t,1H), 7.36(t,1H), 7.08(d,1H), 4.68(brs.2H), 4.01(S,2H), 3.83(s,3H), 2.70(s,3H); ESI-MS: 316 m/z.

2.2.3 Methyl 6-amino-5-(2-bromobenzyl)-2-methyl nicotinate (AN-3): Melting point: 344°C; Yield: 65%; TLC [Hexane: ethyl acetate (1:1)]: 0.69; ^{1}HNMR ($CDCl_3$) 7.84 (s, 1 H), 7.61 (d, 1 H), 7.23 (t, 1 H), 7.13 (t, 1 H), 7.01(d, 1H), 4.79 (brs, 1 H), 3.91 (s, 2 H), 3.83 (s, 3 H), 2.70 (s, 3 H); IR (KBr): 3432, 3325, 3151, 2946, 2835, 1701, 1653, 1599, 1251, 660cm^{-1}.ESI-MS: 337 m/z.

2.2.4 Methyl 6-amino-5-(-4-bromobenzyl)-2-methyl nicotinate (AN-4): Melting point: 324°C; Yield: 70%; TLC [Hexane: ethyl acetate (1:1)]: 0.71; ^{1}HNMR ($CDCl_3$) 8.10 (s, 1 H), 7.85 (d, 1 H), 7.12 (d, 1 H), 4.82 (brs, 2 H), 3.96 (s, 2 H), 3.83 (s, 3 H), 2.72 (s, 3 H); IR (KBr): 3289,2922,2852,1722,1606, 1671, 1567, 1488, 1299, 593cm–1; ESI-MS: 337 m/z.

2.2.5 Methyl 6-amino-5-(2-chlorobenzyl)-2-methylnicotinate (AN-5): Melting point:312°C; Yield: 75%; TLC [Hexane: ethyl acetate (1:1)]: 0.59; ^{1}HNMR ($CDCl_3$) 8.10 (s, 1 H), 7.64 (d, 1 H), 7.20 (m, 2 H), 4.82 (brs, 2 H), 3.96 (s, 2 H), 3.83 (s, 3 H), 2.72 (s, 3 H); IR (KBr): 3473, 3307, 3125, 2924, 2853 cm^{-1}; ESI-MS: 291 m/z.

2.2.6 Methyl 6-amino-5-(3-Bromobenzyl)-2-methyl nicotinate (AN-6): Melting point: 279°C; Yield: 65%; TLC [Hexane: ethyl acetate (1:1)]: 0.62; ^{1}H NMR ($CDCl_3$) 8.10 (s, 1 H), 7.41 (d, 2 H), 6.98 (d, 2 H), 4.82 (brs, 2 H), 3.96 (s, 2 H), 3.83 (s, 3 H), 2.72 (s, 3 H); IR (KBr): ESI-MS: 337 m/z.

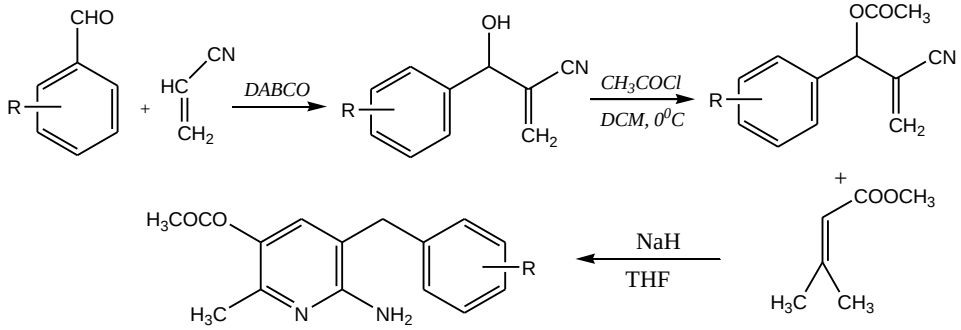
2.2.7 Methyl 6- amino-(3-flurobenzyl)-2-methylnicotinate (AN-7): Melting point: 327°C; Yield: 69%TLC [Hexane: ethyl acetate (1:1)]: 0.64; ^{1}HNMR ($CDCl_3$) 8.05(s, 1H), 7.05(m, 1H), 6.77(s, 1H), 4.67(brs, 2H), 3.96(s, 1H), 3.89(s, 3H), 2.53(s, 3H); IR (KBr): 3452, 3323, 3128, 2947 cm^{-1};ESI-MS: 275 m/z.

2.2.8 Methyl 6-amino-(4-methylbenzyl)-2-methylnicotinate (AN-8): Melting point: 362°C; Yield: 65%; TLC [Hexane: ethyl acetate (1:1)]: 0.56; ^{1}HNMR ($CDCl_3$) δ8.05(s, 1H), 7.11(s, 2H), 4.83(brs, 2H), 3.96(s, 1H), 3.89(s, 3H); 2.53(s, 3H), 2.34(s, 3H); IR (KBr): 3289, 2982, 2923, 2207, 1908 cm^{-1}; ESI-MS: 271 m/z.

2.2.9 Methyl 6-amino-(4-ethylbenzyl)-2-methylnicotinate (AN-9): Melting point: 315°C; Yield: 68%; TLC [Hexane: ethyl acetate (1:1)]: 0.65; ^{1}HNMR ($CDCl_3$) δ8.05(s, 1H), 7.18(d, 1H), 6.98(d, 1H), 4.8(brs, 2H), 3.96(s, 1H), 3.89(s, 3H), 2.60(m, 2H), 2.53(s, 3H), 1.25(t, 3H); IR (KBr): 3484, 3303, 3119, 2963, 2928, 2211 $cm^{-1;}$ ESI-MS: 286 m/z

2.2.10 Methyl 6-amino-(4-isopropylbenzyl)-2-methyl nicotinate (AN-10): Melting point: 275^{0}C; Yield: 69%; TLC [Hexane: ethyl acetate (1:1)]: 0.70; ^{1}HNMR ($CDCl_3$) δ8.05(s, 1H), 7.15(s, 1H), 7.18(s, 1H), 4.74(brs, 2H), 3.96(s, 2H); 3.89(s, 3H), 2.87(m, 1H), 2.53(s, 3H), 1.25(m, 3H); IR (KBr): 3485, 3307, 3119, 2957 cm^{-1};ESI-MS: 299 m/z.

Scheme 1: Synthesis newer 2-amino nicotinate derivatives (AN-1 to AN-10)



Newer 2-amino nicotinate derivatives (AN-1 TO AN-10)

Table 1: Physical constant of newer 2-amino nicotinate derivatives (AN-1 to AN-10)

Compd	R	M.F	M.W	M.P	R_f	% Yield
AN-1	2-trifluro	$C_{16}H_{15}F_3N_2O_2$	324.30	299^{0}C	0.64	67.2
AN-2	2,5-dimethoxy	$C_{17}H_{20}N_2O_4$	285.32	360^{0}C	0.78	62.4
AN-3	2-bromo	$C_{15}H_{15}BrN_2O_2$	335.20	344^{0}C	0.69	69.4
AN-4	4-bromo	$C_{15}H_{15}BrN_2O_2$	335.20	324^{0}C	0.71	71.8
AN-5	2-chloro	$C_{15}H_{15}ClN_2O_2$	290.74	312^{0}C	0.59	73.4
AN-6	3-bromo	$C_{15}H_{15}BrN_2O_2$	335.20	279^{0}C	0.62	70.6
AN-7	3-fluro	$C_{15}H_{15}FN_2O_2$	274.29	327^{0}C	0.64	65.4
AN-8	4-methyl	$C_{16}H_{18}N_2O_2$	270.33	362^{0}C	0.56	68.5
AN-9	4-ethyl	$C_{17}H_{20}N_2O_2$	284.35	315^{0}C	0.65	69.7
AN-10	4-isopropyl	$C_{18}H_{22}N_2O_2$	298.38	275^{0}C	0.70	7.2

3. Biological Evaluation

The animals used in the examination were sheltered in congruence of the Chalapathi Institute of Pharmaceutical Sciences, Guntur, A.P; which follows the guidelines and regulation set by the committee for the control and administration of experiments on animals (CPCSEA), Ministry of social justice and empowerment, Government of India. The studies were attempted with previous approval from the Institutional Animal Ethics committee (Ref. No. 13/IAEC/CLPT/2016-17) and ultimate care was taken to establish that the animals were handling in the most kind and satisfactory manner. Carrageenan-induced rat paw edema method employing Zeitlin's apparatus was used to determine the anti-inflammatory activities of the newly synthesized newer 2-amino nicotinate derivatives AN-1 to AN-10.Pregnant females were eliminated.

3.1 Anti-Inflammatory Activity

3.1.1 Materials

Carrageenan from Sigma-Aldrich Chemicals, USA, whereas sodium CMC was of Merck grade and the required saline (Core Health Care) was purchased from a local supplier (National Scientific Pharmaceuticals, Guntur). Indomethacin used as a standard drug purchased form Research Lab fine Chem Industries.

3.1.2 Preparation of sodium CMC suspension: 1gm of sodium CMC was triturated in 100 ml of distilled water to give the required stock suspension of sodium CMC. This stock suspension was used for suspending all the test compounds as well as the standard drug.

3.1.3 Experimental procedure: Albino rats of either sex, weighing between 150-200 gm, supplied by Chalapathi Institute of Pharmaceutical Sciences, Guntur were divided into twenty seven groups of six animals each. All these groups were kept for fasting overnight and only allowed water adlibitum.

0.05 ml of 1% carrageenan suspension was slowly injected subcutaneously into the subplantar region of the left hind paw to produce inflammation in all the groups. Groups III to XXVII were treated with 2-amino nicotinate derivatives AN-1 to AN-10 (10 mg/kg) after carrageenan administration and the time gap is at an interval of 0.5, 1, 2, 3, 4 and 6 h. Group I used as carrageenan treated control was given only 1% sodium CMC suspension (1 ml/kg) whereas group II received Indomethacin (2 mg/kg). All these doses were administered orally and the induced paw

edema in each group was measured to assess the anti-inflammatory activity.

3.1.4 Measurement of paw thickness: Before carrageenan injection, the thickness of both the paws of each rat was measured using Zeitlin's constant load lever method. The paws thickness was also measured in a similar way after carrageenan injection at time intervals 0, 0.5, 1, 2, 3, 4 and 6 h. The dose selection for the compound in the preliminary screening is usually 5 times the dose of the standard drug Indomethacin, which was used at a dose of 2 mg/kg.

The percent increase at each time interval was determined by using the formula: Yt-Yo / Yo×100 Yt = Paw thickness at time t hours (after injection), Yo = Paw thickness at time 0 hours (before injection)

The percent inhibition of paw oedema thickness was calculated by using the formula: Percentage inhibition = [1- Yt/Yc] × 100

Where Yt= Average increase in paw thickness in groups tested with 2-amino nicotinate derivatives AN-1 to AN-10 and the standard.

Yc= Average increase in paw thickness in control

The results of anti-inflammatory activity of indomethacin and 2-amino nicotinate derivatives AN-1 to AN-10 tested are shown in Table 2.

Table 2: Percentage inhibition in paw thickness at various time intervals

Compd code	% inhibition in paw thickness at various time intervals					
	0.5hr	1hr	2hr	3hr	4hr	6hr
AN-1	18 ± 1*	20 ± 2	62 ± 1	70 ± 1**	90 ± 1	94 ± 1
AN-2	10 ± 1*	14 ± 2	47 ± 1	56 ± 2	84 ± 2	87 ± 1
AN-3	18 ± 1	22 ± 2**	66 ± 1	71 ± 2	89 ± 2	93 ± 2*
AN-4	19 ± 1	22 ± 1	57 ± 1**	67 ± 1	96 ± 1	97 ± 2
AN-5	18 ± 1	22 ± 2**	66 ± 1	71 ± 2	89 ± 2	93 ± 2*
AN-6	17 ± 1	20 ± 2*	54 ± 2	62 ± 2*	89 ± 1	90 ± 1*
AN-7	20 ± 1	24 ± 1	65 ± 1	75 ± 1*	94 ± 1	95 ± 2
AN-8	08 ± 1**	13 ± 1*	44 ± 1	54 ± 1	83 ± 1	84 ± 1
AN-9	03 ± 1	07 ± 1**	39 ± 2	48 ± 1	73 ± 1	74 ± 2
AN-10	08 ± 1**	13 ± 1*	44 ± 1	54 ± 1	83 ± 1	84 ± 1
Indomethacin	21± 1	26 ± 1	58 ± 1	66 ± 1	95 ± 2	98 ± 1

Values are expressed as mean ± (n=6); P*<0.05, P**<0.01 compared to control, Student t-test (Unpaired); Value for the control group in all the cases is zero.

3.2 Analgesic Activity:

Tail immersion method is based on the observation that morphine-like drugs selectively prolong the reaction time of the typical tail withdrawal reflex in mice. Albino rats were divided in twenty-six groups each containing six animals. The tail of mice was immersed (12cm) in warm water kept constant at 55 ^{0}C.Their action time was recorded by stopwatch (the reaction time is the time taken by the rats to flick their tails).The latent period of the tail flick response will be determined before and 30, 60, and120 min after drug administration. Diclofenac sodium is used as standard in analgesic activity. The results were expressed as mean ±SEM for six animals in each group analgesic activityare shown in Table 3.

Table 3: Analgesic activity of synthesized compounds at various time intervals

Compd code	Reaction time(sec)		
	After30min	After60min	After120min
AN-1	5.87 ± 1.1	10.34 ± 0.09∗	16.37 ± 2.0∗
AN-2	5.67 ± 0.8	7.44 ± 0.05	10.03 ± 2.5
AN-3	5.17 ± 0.9	10.46 ± 0.02	18.42 ± 1.9
AN-4	5.70 ± 1.0	11.55 ± 0.01∗	20.25 ± 1.6∗
AN-5	6.75 ± 1.1	12.65 ± 0.02∗	18.80 ± 1.7∗
AN-6	6.78 ± 1.3	11.07 ± 0.02	18.75 ± 2.4
AN-7	5.80 ± 1.4	12.12 ± 0.02	19.37 ± 2.4
AN-8	4.42 ± 0.7	7.60 ± 0.06	10.32 ± 2.0
AN-9	5.72 ± 1.2	6.05 ± 0.02	8.20 ± 2.4
AN-10	5.83 ± 1.6	6.61 ± 0.08	9.35 ± 1.6
Control	5.43 ± 1.7	5.29 ± 0.9	6.30 ± 1.2
Diclofenac sodium	5.07 ± 1.6	10.60 ± 2.0	18.83 ± 2.4

All values are expressed as means ± SEM (n=6), $*P<0.05$ versus control.

4. Results and Discussion

4.1 The compounds were synthesized as per the scheme:

The solution of NaH in anhydrous THF was added the enamino ester, methyl 3-methylbut-2-enoate dissolved in anhydrous THF at room temperature under N_2 atmosphere, and the mixture was stirred at the same temperature. Then, an acetylated Baylis–Hillman nitrile dissolved in anhydrous THF was addedat room temperature and extracted with ethyl acetoacetate. The proposed structures of all the synthesised compounds were well supported by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the newly synthesized newer 2-amino nicotinate derivatives AN-1 to AN-10 has been evaluated for their anti-inflammatory and analgesic activities.

The anti-inflammatory activity of synthesized newer 2-amino nicotinate derivatives AN-1 to AN-10 has been evaluated by using carrageenan-induced rat paw edema method. The results of the evaluation have been viewed by taking Indomethacin as the standard drug. From all the compounds AN-1, AN-3, AN-4, AN-5, AN-6 and AN-7 having a chloro fluoro, and bromo group at *para* and *ortho* positions were found to be potent in anti-inflammatory activity which is comparable to standard. Also the presence of *para* and *ortho* substituted halogens in the compound results in enhanced biological activities. This significant increase in biological activities is attributed due to the electron withdrawing nature of halogens, which ultimately results in enhancement in lipophilicity. This enhanced lipophilicity could facilitate the penetration or passage of these compounds across the biological membrane easily.

The analgesic activity of the newly synthesized 2-amino nicotinate derivatives AN-1 to AN-10 has been evaluated by using Tail immersion method. The results of the evaluation have been viewed by taking Diclofenac sodium as the standard drug. From all the compounds, AN-1, AN-3, AN-4, AN-5, AN-6 and AN-7 having electron withdrawing groups were found to be potent in analgesic activity which is comparable to standard.

5. Conclusion

In this study, newer 2-amino nicotinate derivatives AN-1 to AN-10 were synthesized by the Baylis Hillman Reaction by treating NaH in anhydrous THF was added methyl 3-methylbut-2-enoate and the mixture was stirred at the same temperature. Then, an acetylated Baylis–Hillman nitrile dissolved in anhydrous THF was added at room temperature and extracted with ethyl acetoacetate. The results of anti-inflammatory and analgesic activity revealed that the compounds AN-1 to AN-10exhibited moderate to considerable activity when compared with reference standard Indomethacin and Diclofenac sodium. Compounds AN-1, AN-3, AN-4, AN-5, AN-6 and AN-7having the electron withdrawing groups like the halogens showed maximum activity and this is consistent with the literature reports that such groups enhance the lipophilic properties of the molecule.

Conflict Of Interest: None

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