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Synthesis and characterization of novel halogens substituted coumarin-Aldehyde

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ABSTRACT

Coumarins have a long history of having number of pharmacological activities such as anticoagulant, antithrombotic, antimutagenic, vasodilator, LOX and CLOX inhibitors and it can also used in treatment of edema. The recent success of Coumarins as anti-inflammatory and anticoagulant has further highlighted the importance of this class in medicinal chemistry. Systematic investigation of this class of compound revealed that coumarin derivatives containing pharmacophore agent plays an important role in medicinal chemistry. This prompted to me, to synthesize new derivatives of Coumarins, 4-Chloro-3-coumarinaldehyde was reacted with halogens substituted aniline and rectified spirit to obtain a new series of 4-chloro-(3-substituted-phenylimino)-methyl-coumarin. A total of 6 compounds were synthesized. Their structures were confirmed by, ^{1}H-NMR and Mass spectroscopy.

Key words: Anti-coagulant, Vasodilators, LOX inhibitors, edema, coumarin, ^{1}H-NMR, Mass.

1. INTRODUCTION

Coumarins owe their class name to 'Coumarou', the vernacular name of the tonka bean (*Dipteryx odorata* Willd, Fabaceae), from which coumarin it was isolated in 1820 **[1]**. Coumarins classified as a member of the benzopyrones family of compounds, all of which consist of a benzene ring joined to a pyrone ring. The benzopyrones can be subdivided into the benzo-alfa-pyrones to which the coumarins belong and the benzo-gama-pyrones, of which the flavonoids are principal members **[2]**. There are four main coumarin sub-types: the simple Coumarins, furanocoumarins, Pyranocoumarin and the pyrone-substituted Coumarins. The simple Coumarins (e.g. coumarin, 7-hydroxycoumarin and 6, 7-dihydroxycoumarin), are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides. Furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus, divided into linear or angular types with substituent at one or both of the remaining benzoid positions. Pyranocoumarin members are analogous to the furanocoumarins, but contain a six-membered ring. Coumarins substituted in the pyrone ring include 4-hydroxycoumarin **[3]**.The synthetic compound, warfarin, belongs to this coumarin subtype. Coumarin is water insoluble; however 4-hydroxy substitution confers weakly acidic properties to the molecule that makes it water soluble under slightly alkaline conditions. The coumarin structure is derived from cinnamic acid via ortho-hydroxylation, trans-Cis isomerisation of the side chain double bond, and lactonisation **[4]**. The Trans form is stable and could not cyclist, therefore, there should be isomerisation of some sort and the enzyme isomerase is implicated. The Cis form is very unstable, therefore, will tend to go to the Trans configuration. Glucose is a good leaving group which assists in the Cis-trans transformation **[5, 6]**. A specific enzyme found in *Melilotus Alba (Leguminosae)* specifically hydrolyses the Cis-glycoside (beta-glycosidase). This biosynthesis pathway should be followed by all coumarins oxygenated at position-7. Umbelliferone, esculetin and scopoletin are the most widespread coumarins in nature **[7]**.

2. MATERIAL AND METHODS

2.1. Materials

2.1.1. Chemicals and Reagents

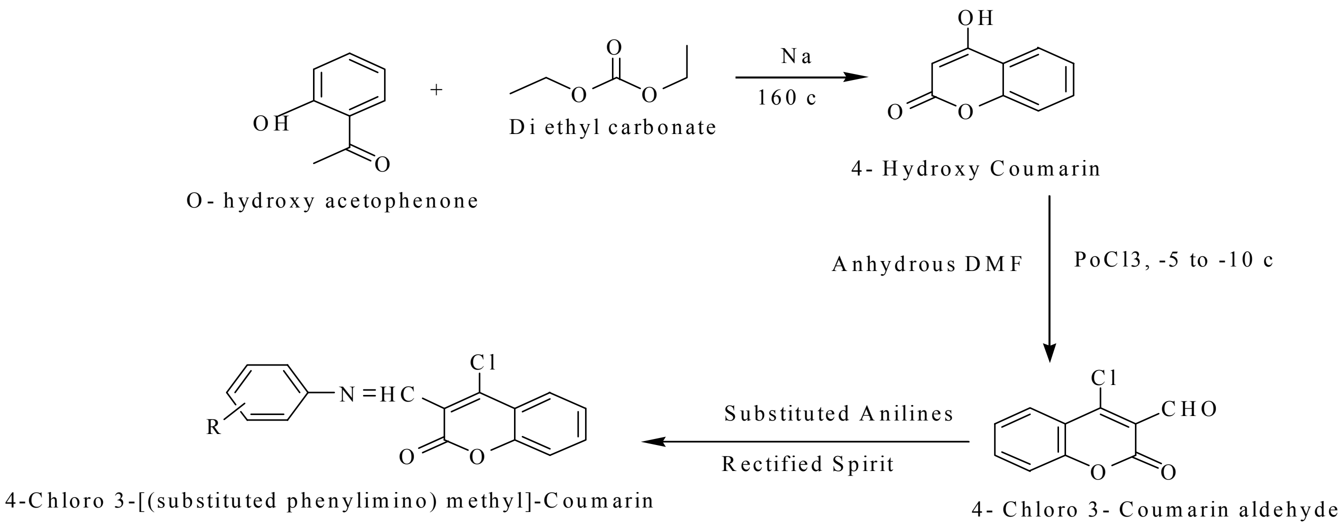
O-hydroxyacetophenone, sodium, diethyl carbonate, xylene, NaOH, 4-hydroxycoumarin, anhydrous DMF, $POCl_3$, halogens substituted aniline, rectified spirit, methanol, Dichloromethane, n-hexanol, petroleum ether

2.1.2. Instruments:

MAL-DI-4800 instrument for Mass Spectra and DRX-300 Spectrometer for ^{1}H-NMR Spectra

2.2. Methodology

Figure -1: Scheme of Synthetic Work



2.2.1. Preparation of 4-hydroxycoumarin

To a mixture of *o*-hydroxyacetophenone (10.0 mol), sodium (25.0 mol) and diethyl carbonate (30.0 mol), mixed well and heated at 160^0c with constant stirring. The mixture was diluted with xylene (30 ml.) and further heated at 160^0C for 1 hrs. and then the mixture was poured into cold water (400 ml.). NaOH was used to make the mixture alkaline and mixture was stirred with diethyl ether. After which the aqueous phase was collected and then acidified with HCl. Product was filtered, washed with ice cold water and dried in vacuum desicator.

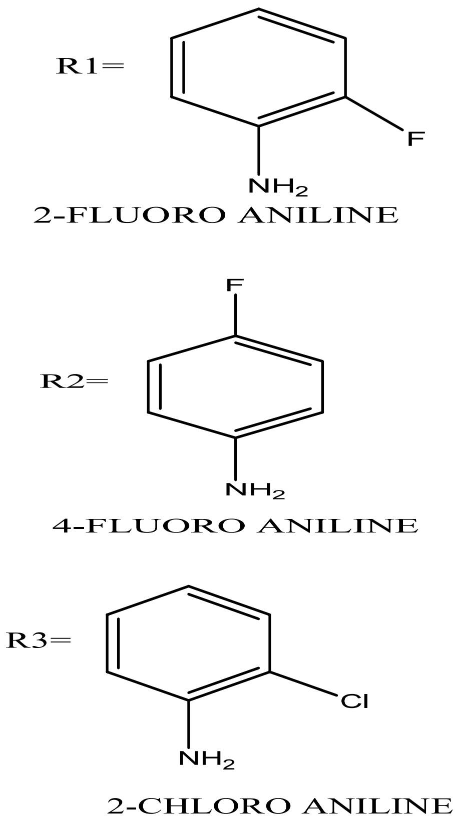
2.2.2. Preparation of 4-chloro-3-coumarinaldehyde

To a stirred mixture of 4-hydroxycoumarin (0.06 mol) in anhydrous DMF (0.6 mol) was added to which POCl3 (0.18 mol) was added drop wise at -10 to -5 ^{0}C. Mixture was then stirred for 1hrs. at room temperature and heated and stirred for 2 hrs. at 60 ^{0}C. After the reaction was completed, the mixture was kept overnight at 0 ^{0}C. The separated pale yellow solid was collected by filtration and washed successively with Na_2CO3 solution (5%) and water and was dried in air.

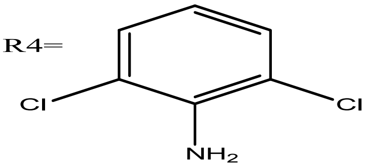
2.2.3. Preparation of novel Halogens substituted coumarin-aldehyde

4-Chloro-3-Coumarinaldehyde, (0.005 mol), halogens substituted aniline (0.005 mol) and rectified spirit (20 ml.), was reflux for 1 hrs. Water was then added. The oil that separated was induced to crystallize by rubbing with glass rod and the solid was collected by filtration. After washing well with cold ethanol (88%), the crude product was dried and recrystallised from aq. methanol. Compounds were prepared similarly by using different Halogens substituted anilines *[8]*.

Figure -2: Halogens Substituted Anilines.

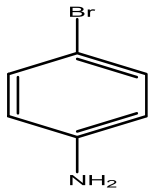


R4=



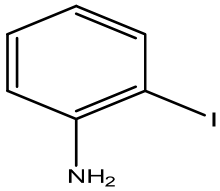
2,6-DICHLORO ANILINE

R5=



4-BROMO ANILINE

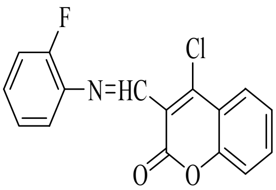
R6=



2-IODO ANILINE

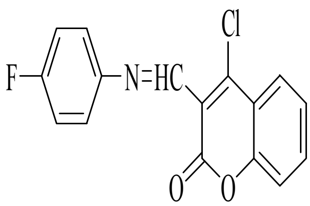
Figure -3: Chemical Structure & Name of Synthesized Compounds

C.1- (Compound.1.)



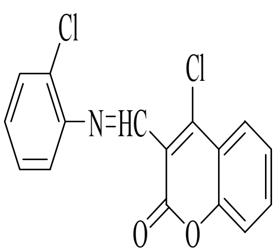
4- Chloro- 3-[(2-fluorophenylimino)methyl]- Coumarin

C.2-(Compound.2.)



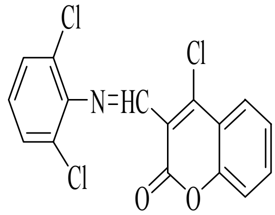
4- Chloro- 3-[(4-fluorophenylimino)methyl]- Coumarin

C.3-(Compound.3.)



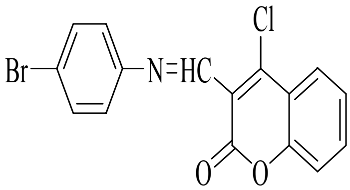
4- chloro- 3 -[(2-chlorophenylimino)methyl]- Coumarin

C.4-(Compound.4.)



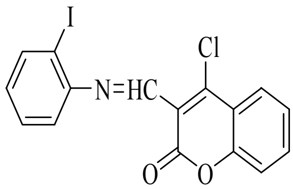
4- Chloro 3-[(2,6-dichloro phenylimino)methyl]- Coumarin

C.5- (Compound.5.)



4- Chloro- 3- [(4-bromophenylimino)methyl]- Coumarin

C.6- (Compound.6.)



4- Chloro- 3-[(2-iodophenylimino)methyl]- Coumarin

2.2.4. Reaction Monitoring

Synthetic procedure employed were monitored by thin layer chromatography (TLC) employed 1.5×5 cm. pre-coated plates. Solvent system of Methanol-Dichloromethane mixtures of varying polarity were used to monitor the reactions. The dried plates after development were visualized in iodine chamber.

2.2.5. Melting Points Estimation

Melting points were estimated with MAC melting points apparatus in open capillaries and are uncorrected.

TLC Snaps of Synthesized Compounds

Figure - 4: C.1- 4-Chloro-3-(2-fluoro phenylimino)-methyl coumarin, R_f: 0.58

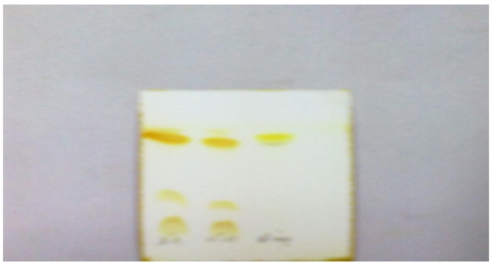


Figure - 5: C.2- 4-Chloro-3-(4-fluoro phenylimino)-methyl coumarin, R_f: 0.68

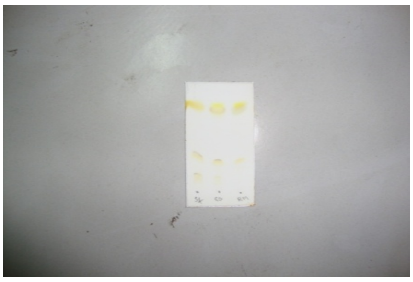


Figure - 6: C.3- 4-Chloro-3-(2-chloro phenylimino)-methyl coumarin, R_f: 0.68

Figure - 8: C.5- 4-Chloro-3-(4-bromo phenylimino)-methyl coumarin, R_f: 0.62

Figure - 7: C.4- 4-Chloro-3-(2, 6-dichloro phenylimino)-methyl coumarin, Rf: 0.54

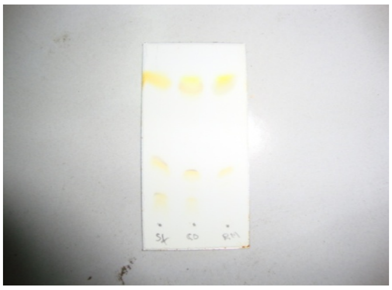


Figure - 9: C.6- 4-Chloro-3-(2-iodo phenylimino)-methyl coumarin, R_f: 0.65

Table-1: Physicochemical characterization of Synthesized Compounds

Physicochemical Parameters	Compound-1	Compound-2	Compound-3	Compound-4	Compound-5	Compound-6
Mol. Formula	$C_{16}H_9O_2ClNF$	$C_{16}H_9O_2ClNF$	$C_{16}H_9O_2NCl_2$	$C_{16}H_9O_2NCl_3$	$C_{16}H_9O_2NClBr$	$C_{16}H_9O_2NClI$
Mol. Weight	377.69	377.69	408.65	501.60	498.60	391.65
Melting Points	190^0c	205^0c	170^0c	185^0c	215^0c	210^0c
% Yield	77.50 %	78.50 %	67.6 %	85.0 %	72.6 %	66.5 %
R_f Value	0.58	0.68	0.68	0.54	0.62	0.65

3. RESULT AND DISCUSSION

3.1. Compound C.1

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z = 377.08 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.02 1H) methyl, δ (7.11 4H) phenyl, δ (7.02 4H) phenyl.

3.2. Compound C.2

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z

= 377.08 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.14 1H) methyl, δ (6.88 4H) phenyl, δ (7.2 4H) phenyl.

3.3. Compound C.3

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z = 408.65 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.1 1H) methyl, δ (7.11 4H) phenyl, δ (8.0 4H) phenyl.

3.4. Compound C.4

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z = 501.60 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.8 1H) methyl, δ (7.11 4H) phenyl δ (8.0 4H) phenyl.

3.5. Compound C.5

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z = 498.65 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.2 1H) methyl, δ (7.6 4H) phenyl, δ (8.3 4H) phenyl.

3.6. Compound C.6

Mass spectra: The mass spectra of compound-2 by MALDI-technique. The molecular mass peak of proposed compound is found as m/z = 391.65 ^{1}H-NMR spectra: The ^{1}H -NMR spectra in $CDCl_3$ at 200 MHz δ (3.1 1H) methyl, δ (7.3 4H) phenyl, δ (8.0 4H) phenyl.

The above results of Mass and NMR spectral analysis confirm the six structure of 4-chloro-3-[(substituted phenylimino)-methyl] coumarin which synthesized by various halogens substituted anilines.

4. CONCLUSION

It has been reported that naturally occurring coumarin derivatives such as 2*H*-1-benzopyran-2-one, 4-hydroxycoumarins shows different pharmacological activities which are clinically important. The data reported showed that the effect of variation in chemical structure was rather unpredictable. Structural modifications lead to uniform alteration in activity in all tests. The substitution which appeared to be most important for high order of activity in the number of test was the 3-chloro phenylimino group.

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5. REFERENCES

1. Bruneton J. Hampshire U K, **Intercept Ltd.**1999; 4(2): 263-277.
2. Ojala T. PhD Thesis, **University of Helsinki, Helsinki,** Finland. 2001.
3. Keating G and O Kennedy R. Synthesis & pharmacological evaluation of coumarin derivatives as cannabinoid receptor antagonist & inverse agonist & reported 5-sub. 3-benzylcoumarin derivatives showed affinity to cannabinoid CB_1 & CB_2 receptors. **John Wiley & Sons.** 1997; 2(3): 66-75.
4. Murray RDH, Mendez J and Brown SA. Synthesis & biological evaluation of novel coumarin based inhibitors of CDC25 inhibitors. **John Wiley.,** 1982; 2(4): 45-56.
5. Constantinou AI, Kamath N and Hurley JS. Design & synthesis of stilbene-coumarin hybrid compounds & compounds has been reported as anti-cancer activity. **European Journal of Canada.** 1998; 34(3): 1927-1938.
6. Egan D, O Kennedy R, Moran E, Cox D, Prosser E and Thornes RD. Synthesis of a novel series of 5-(substituted)-aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines & pharmacological evaluation reported as a novel anti-inflammatory & analgesic effects**. Journal of Drug Metabolism Review.**1990; 22(2): 503-515.
7. Guilet D, Seraphin D, Rondeau D, Richomme P and Bruneton J. Design & synthesis of novel sulfonamides containing 4-azido methyl coumarin & evaluated for anti-microbial studies. **International Journal of chemistry.** 2001; 28(2): 571-583.
8. Bairagi S, Bhosale A and Deodhar MN. Design & synthesis of Schiff's bases of 4-chloro-3-coumarin aldehyde & evaluated for anti-microbial activity. **European Journal of Chemistry.** 2009; 6(2): 759-771.